NUFFIELD COUNCIL ON BIOETHICS

Genome editing

an ethical review

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Terms of reference

The terms of reference for the working group are:

1. To identify and define ethical questions relating to developments in genome editing research.

2. To review institutional, national and international policies and provisions relevant to genome editing, and to assess their current and likely future significance.

3. To deliberate and to draw conclusions, as appropriate, about the nature of the ethical questions raised and how they might most suitably be addressed.

4. To report on these matters and to make recommendations, as appropriate, for further initiatives by the Council or by other identified bodies, or for the development or revision of policy or legislation.

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Introduction

1. It seems as though genome editing is everywhere. In a relatively short time, particularly since the emergence of the CRISPR-Cas9 system in 2012, techniques for making precisely targeted alterations to DNA sequences in living cells have not only preoccupied life science journals, but have also featured in mainstream news. They have been implicated in stories of revolutionary medical advance and genetically altered food, and in the business pages, where the battle over the intellectual property rights to the underlying technology, and the prospects of companies developing genome editing treatments and products, have been matters of continual intrigue and speculation.

2. While the scientific merits are overt, the practical and ethical significance of these recent developments is far harder to discern. While the use of genome editing techniques has spread across biological research, including microorganisms, plants, animals and human cells, the extent to which the potential applications can be understood in relation to prevailing norms and managed through existing governance measures has not been extensively examined. As a rapidly established (though continually developing) research technique, one that is at the foundation of diverse emerging biotechnologies, there is concern that genome editing science and innovation are moving ahead of public understanding and policy.

3. The Nuffield Council's terms of reference charge it "to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern." In 2015, convinced that genome editing had the potential to raise such questions, the Council agreed to undertake a programme of work and established an interdisciplinary working group to gather evidence and to deliberate in relation to these matters. The present publication is the output of the first stage of this work. It addresses conceptual and descriptive issues regarding genome editing and identifies the key ethical questions that arise.

4. This first report is intended to provide the platform for a second stage of the project, which will deal with normative – evaluative and prescriptive – questions in relation to one or more closely defined areas in which genome editing has (or is expected to have) an impact. In other words, the present report starts with a technical development and looks at its possible impacts; the second part will take a domain of challenges facing human ingenuity and explore the possible role that genome editing may and should have. It will explore this in the context of other technologies and other responses to the challenges framed, in order to consider both the value and the opportunity costs of different approaches.

5. Here, therefore, is the Council's digest of and reflection on the evidence that it has gathered to date. The report contains no explicit recommendations for action, although it does contain a number of judgements and conclusions. The Council will reflect on these, and on the response of others to these, as it proceeds with its deliberations in the areas that are marked out in the conclusion to this report.

Section 1

Genome editing

Section 1 – Genome editing

Overview

This first section examines the concept of genome editing and its origins in biological research. Genome editing is set in the context of the range of techniques that the life sciences have afforded to allow deliberate influence over organisms and biological materials. It is characterised by its level of action (nucleotide sequences and epigenetic marks), the precision with which it may be targeted, and its controllability.

To elucidate the mode of action of genome editing techniques, the role of DNA (and RNA) in organisms is described and the concepts of 'gene', 'genome' and 'epigenome' are discussed. The difficulties involved in defining these, and the different registers in which they are presented (molecular, informational, functional, genealogical, etc.) are noted. The reproductive re-assortment of DNA and sources of errors are described, as they may lead to variation and, in some cases, to disease. The complexity of associating genetic variation with phenotypic outcomes is noted.

Current techniques of genome editing are described in the context of prior art. Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs) and the CRISPR-Cas9 system make double-stranded breaks in DNA that cells repair using inbuilt pathways. The section outlines how this may be harnessed to 'knock out' genes through non-homologous end-joining, or to insert or remove specific DNA sequences through homology directed repair. The relative advantages and limitations of the different existing approaches, including epigenome editing with Cas9 derivatives, are discussed and some areas of current uncertainty and continuing research are identified. Given the current pace of development it is anticipated that genome editing techniques will continue to be refined and new techniques emerge. Hence, the emphasis in this report will be on what can be achieved using genome editing techniques, rather than the techniques themselves.

The concept of genome editing

1.1 People have long sought and used scientific knowledge to improve the conditions of human life. From breeding crops and the domestication of livestock to modern health care, the biological sciences underpin the possibility of human beings exercising ever greater levels of control over the biosphere, including their environment, the other living beings with which they share it and their own bodies. Contemporary molecular biology affords a particularly powerful set of tools that form the basis of a range of technologies in fields as diverse as medicine, agriculture, industrial production, and environmental management. What we will refer to as 'genome editing' is the practice of making targeted interventions at the molecular level of DNA or RNA function, deliberately to alter the structural or functional characteristics of biological entities. These entities include complex living organisms, such as humans and animals, tissues and cells in culture, and plants, bacteria and viruses. Characteristics of many kinds, from the colour or number of blooms in flowering plants, to some disease traits in animals and plants, can be altered, though the extent to which, and ease with which, such alterations can be made is highly variable.

1.2 Targeted alterations may be accomplished in different ways, including through the use of new and emerging techniques such as the CRISPR-Cas9 system described below. In the future, they may be accomplished in ways that have not yet been described or even envisaged. Nevertheless, although recent advances have meant that genome editing has become highly effective in many research contexts (depending on the system used, the conditions of use, and the model organism) there remains some variation in how fully the underlying aims (of deliberate alteration of biological characteristics) have so far been realised.

1.3 Throughout this report we refer to 'genome editing' rather than 'gene editing' (although the latter term is also in use) because the concept of genome editing is not limited to genes. For our purposes, 'genome editing' also includes making alterations to non-coding regions of genomes and to epigenomes (in order to modify whether all or part of the genome is active or silent, and to 'tune' the level of activity). Genome editing clearly shares features with techniques of 'genetic engineering' that have been developed and used over the last forty years (in plant breeding, for example) as well as with more recent micromanipulation techniques for cell reconstruction (for

example, 'cloning' and mitochondrial donation).1 By what principles or according to what criteria these different biological interventions should be delineated, and what moral significance should attach to those distinctions, are among the important questions addressed in this review.

Gene, genome and epigenome

1.4 There is no generally agreed definition of the term 'genome'. On any understanding, however, genomes comprise the chemical deoxyribonucleic acid (DNA) or, in the case of some viruses, the related chemical ribonucleic acid (RNA).[2] DNA is found in almost all cells of living organisms; it plays a crucial role in their development and functioning, and is centrally involved in the transmission of their properties between generations. DNA is often a very long molecule, a polymer, consisting of a sequence of four different sub-units, called nucleotides, arranged in a particular order. This order, or sequence, largely determines the important biological roles of the molecule. DNA comes in a double strand, forming the iconic double helix structure.[3] The double strand can separate, each strand becoming a template for a new second strand, the process that enables identical sequences of DNA to be replicated when cells divide. Genome lengths range from a few thousand nucleotides in the case of bacteria and viruses to several billions in the case of mammals. Some genomes are larger still. The human genome comprises 3.23 billion nucleotides; the wheat genome is about five times this size.

1.5 The term 'genome' may be used either to refer to the particular sequence of nucleotides in an organism or in a specific kind of organism, or to the material object that they partly constitute.[4] In the latter sense many genomes consist of a set of *chromosomes*, in which the DNA helix is tightly wound around proteins called histones. Modifications to the histones, or alternatively the attachment of additional chemical parts to the nucleotides, is often crucial in determining which parts of the genome are activated or suppressed. These modifications may be passed on from one generation to the next: heritable changes that are not based on changes to the nucleotide sequences are referred to as 'epigenetic' changes. The genome includes *genes*, regions that can direct the production of specific proteins or parts of proteins.[5] Proteins are the molecules that make up most biological structures, and also that direct many chemical processes; they are sometimes thought of as the executive molecules in an organism. There are also regions of the genome that help to control which genes are active in the organism at certain times or in certain conditions. Finally, there are regions that appear not to be functional at all, though the extent of this phenomenon is hotly debated.[6] The term 'genome' is often used to refer only to the nucleic acid in the cell nucleus, a membrane-enclosed compartment inside the cell[7]; however, at a cellular

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1 The Council's 2012 report, *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* (available at: http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf), noted the similarities between different biological techniques capable of modifying the human germ line and advised that a fuller discussion of such techniques would benefit the wider policy debate.

2 The genome of RNA viruses – those that use RNA instead of DNA as their genetic material – usually comprises a single strand of RNA, although some RNA viruses are double-stranded. It is a matter of debate whether viruses should be described as living organisms.

3 Some DNA viruses contain a single-stranded (rather than double-stranded) DNA molecule as their genetic material.

4 For the functional importance of the genome as a material object, see Bustin M and Misteli T (2016) Nongenetic functions of the genome *Science* **352**(6286): aad6933, doi: 10.1126/science.aad6933.

5 There are also non-coding genes, i.e. reasonably discrete functional units that are transcribed (into non-coding RNA) in a tissue-specific fashion, like a protein-coding gene, but which do not apparently encode proteins. See: Yang JX, Rastetter RH and Wilhelm D (2016) Non-coding RNAs: an introduction, in *Non-coding RNA and the reproductive system*, Wilhelm D and Bernard P (Editors) (Dordrecht: Springer Netherlands), pp13-32.

6 The ENCODE (Encyclopedia of DNA elements) Project is an international research collaboration that aims to build a 'parts list' of the functional elements of the human genome, and other genomes (https://www.encodeproject.org). There has been some controversy over whether the epigenomic marks characterised by ENCODE can be deemed to be functional. See, for example, the critique in Graur D, Zheng Y, Price N, *et al*. (2013) On the immortality of television sets: "function" in the human genome according to the evolution-free gospel of ENCODE *Genome Biology and Evolution* **5**(3): 578-90, available at: http://gbe.oxfordjournals.org/content/5/3/578.

7 This does not apply to all cells: many single-celled organisms, bacteria and archaea, lack a distinct nucleus. In addition, certain cell types – mature red blood cells in mammals, which have the single specialised function of transporting oxygen in haemoglobin – do not contain a nucleus.

or organismal level it may also encompass nucleic acids found in mitochondria, small organelles that provide energy to the cells of most higher organisms, and plastids, found in plants and algae.

1.6 The genome is often described as a code, because those parts of the genome that guide the production of proteins do so by virtue of a precise correlation between nucleotide triplets and amino acids, the chemicals that make up proteins. The process by which proteins are produced involves two stages: first a DNA sequence is 'transcribed' into an RNA molecule, a 'messenger RNA', which is subsequently 'translated' into part of a protein using an intermediate molecule, a 'transfer RNA'. Various changes and rearrangements of the messenger RNA may occur between transcription and translation, so there is no simple correlation between genes and proteins. Proteins typically depend for their production on many genes and a gene can be involved in the production of many proteins. Regions of the genome can be regulated by proteins that cause an associated region to be active, producing an RNA transcript, or silent, so that no RNA transcript is produced.[8]

1.7 Genomes are passed from one generation to the next when organisms reproduce. Sexual reproduction shuffles parental genomes so that offspring receive a new genome that is a unique combination of the two. In sexually reproducing organisms such as mammals, chromosomes come in pairs that are very similar but, importantly, not identical. Each parent contributes one copy of each chromosome to their offspring. Though the particular sequence of DNA that comprises an individual's genome is thereby inherited from the previous generation, the genome is subject to alteration by a number of causes. Within every cell of the organism, whenever a cell grows and divides, it copies its DNA so that each 'daughter' cell has the same genetic code. However, errors in DNA replication occur and, if these are not corrected, mutations may be incorporated. If cell death does not ensue, cells with mutated DNA may be propagated and may lead to pathological states (for example, cancers in humans and animals). DNA can also be damaged by radiation and toxic chemicals, again leading to the incorporation of mutations. Differences may also be introduced through infection: some viruses insert their DNA into their host's DNA (as in the case of human papilloma virus infection that may lead to cervical cancer). As noted above, epigenetic modifications to the genome, which may also be induced by environmental factors such as diet or stress, may thus reflect the developmental history of the organism. Epigenetic modifications do not affect the sequence of nucleotides in the genome but are a central aspect of how the genome functions. In the case of organisms that reproduce sexually, epigenetic changes can result in genes being expressed in a parent-of-origin-specific manner, a phenomenon known as genomic imprinting.[9]

1.8 There are many small variations between any two genome sequences within the same species. Genome sequence variations within protein coding sequences or in regulatory sequences may have specific effects on the ostensible characteristics (the 'phenotype') of an organism and its biological function. Early research, before DNA was identified as the genetic material, was entirely concerned with identifying these differences and their mode of transmission across generations. Such work continues, often under the rubric of 'Mendelian' genetics, after Gregor Mendel, the Austrian monk who pioneered this kind of investigation. Well-known genetic diseases, such as haemophilia or cystic fibrosis, are caused by a single variation in a specific gene and are sometimes referred to as monogenic or Mendelian.[10] All biological traits, including common diseases such as cancer and coronary heart disease, reflect a complex interaction of multiple

[8] Note that the very numerous messenger RNA molecules, regulatory RNAs, and RNAs that may be transcribed but lack an evident biological function, are nucleic acids but are not considered part of the genome. Unlike the genome, which is relatively stable, they are rapidly changing constituents of the cell. They are sometimes referred to collectively as the 'transcriptome'.

[9] Peters J (2014) The role of genomic imprinting in biology and disease: an expanding view *Nature Reviews Genetics* **15**(8): 517-30.

[10] Even monogenic inheritance may, rarely, be more complex than this presentation suggests due to the effects of genetic variants (modifiers) elsewhere in the genome of some individuals. See Chen R, Shi L, Hakenberg J, *et al*. (2016) Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases *Nature Biotechnology* **34**(5): 531-38.

genetic and environmental factors.[11] Proteins (which are encoded by genes) have structural and (as enzymes) catalytic roles, and perform a vast array of functions, orchestrating the activities of other important molecules in the cells. They perform specific activities such as metabolising glucose, responding to hormones, transporting chemicals such as oxygen (haemoglobin), and protecting against infection (antibodies). Most of these functions are causally upstream of the phenotype, and a given protein may contribute to multiple phenotypic effects, a phenomenon known as 'pleiotropy'. This can occur because the function of a particular protein may vary according to when and where it is produced in the organism. As already noted, furthermore, most of the genome (about 98%) does not code for proteins at all. For these reasons, it is often extremely difficult to correlate variations in genes with specific phenotypes, and many variations in phenotype have no determinate association with genetic characteristics. It is important to stress this in order to contradict the belief, sometimes known as 'genetic determinism', that all differences in physical traits, or even in higher order capacities or behaviours, are directly determined by variations at the level of the genome.

Techniques of genome editing

1.9 Genomes are naturally susceptible to alteration and errors occur every time a cell copies its DNA. If these errors are not corrected by the cell, cancer or some other pathology may arise, or they may confer a competitive advantage, becoming the basis for natural selection. In addition, genomes may be altered by infection (for example, by retroviruses) and ionising radiation (for example, in the case of radiotherapy, X-rays and ultraviolet light), which disrupt DNA at locations that may be difficult or impossible to predict. However, these mechanisms are not targeted and so would not be regarded as genome editing.[12]

Recombinant DNA technology

1.10 With the arrival of molecular biology in the second half of the twentieth century, it became possible to alter genomes in controlled ways. In particular, this development was enabled by a new recombinant DNA technology that allowed the cutting and then splicing together of DNA molecules. This was developed first in bacteria and their viruses, and subsequently applied to multi-cellular organisms, including plants and vertebrates.[13] The first 'transgenic' mice (mice containing DNA from another species) were produced in the mid 1970s. Transgenesis became a powerful biological research tool, although its major limitation was that it only allowed genes to be added, and offered no control over where the added genes would be inserted into the genome.

1.11 In 1989 a way was found to introduce directed alterations into the genomes of embryonic stem cells (ES cells) from which entire mice could be generated.[14] ES cells, derived from the inner cell mass of the early embryo, retain the pluripotency of those embryonic cells, meaning that they have the potential to develop into many distinct types of cell in the body. Genetically modified ES cells can, therefore, be re-introduced into the embryo and will contribute to multiple tissues of that individual, including germ cells. This results in germ cells carrying genetic changes that can be used to generate whole animals. Crucially, ES cells with the desired targeted genetic modifications

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[11] This manner of speaking about interactions between genetic and environmental factors passes over many complexities, events that mediate between the effects of genes and environments, including details of transcriptional control, alternate splicing or *in vivo* editing of RNA molecules and the chemical modification of proteins, all of which may alter function and the properties of networks in which these molecules operate. For further discussion, see Burian RM (2004) Molecular epigenesis, molecular pleiotropy, and molecular gene definitions *History and Philosophy of the Life Sciences* **26**(1): 59-80.

[12] For estimates on the mutation rate in humans, see: Callaway E (2015) DNA mutation clock proves tough to set *Nature* **519**(7542): 139-40; Scally A (2016) The mutation rate in human evolution and demographic inference *Current Opinion in Genetics & Development* **41**: 36-43.

[13] Berg P and Mertz JE (2010) Personal reflections on the origins and emergence of recombinant DNA technology *Genetics* **184**(1): 9-17.

[14] See Capecchi MR (2005) Gene targeting in mice: functional analysis of the mammalian genome for the twenty-first century *Nature Reviews Genetics* **6**(6): 507-12. Work leading to this breakthrough was recognised in the 2007 Nobel Prize for Physiology or Medicine, which Mario Capecchi shared with Oliver Smithies and Martin Evans.

can be selected from a vast background of non-targeted cells so the relatively inefficient process of changing the ES cell genome is not a significant obstacle. The gene targeting method initially used to alter mouse ES cells also led to advances in other vertebrates as well as non-vertebrates and plants. However, progress has often been technically challenging and, accordingly, some developments have not occurred until recently. In the case of mammals, for example, ES cells have not been obtained for most species and, even in mice, where the technology is relatively refined, it is time-consuming, expensive, variable, often highly inefficient, and requires a special skill set.[15]

Engineered endonucleases: ZFNs and TALENs

1.12 These limitations justified a continued search for alternative gene targeting technologies that bore fruit with the first reports, in 2005, of zinc finger nucleases (ZFNs) and, in 2010, of transcription activator-like effector nucleases (TALENs). ZFNs and TALENs are proteins that work in a conceptually similar manner, containing one module that can be engineered to recognise a specific DNA sequence and guide a second, attached module to cut the DNA. ZFNs and TALENs are derived, respectively, from mammalian transcription factors (proteins in mammalian cells that bind to DNA and cause a gene to become active) and the plant pathogen, *Xanthomonas* sp. Although their protein frameworks differ, ZFNs and TALENs each contain a set of 'fingers' or 'repeats' that can be designed to recognise a selected DNA sequence with a high degree of specificity. Zinc-finger domains of ZFNs recognise three to four matching base-pairs of DNA; individual TALE repeats recognise a single base-pair. In both cases specificity is provided by combining multiple fingers/repeats and attaching this module to an enzyme that cuts one strand of DNA; ZFNs and TALENs each work in pairs to produce a double-strand break (a break at opposite points in the two entwined strands of the DNA molecule).

1.13 The consequences of double-strand genome breaks are potentially lethal to living cells and are rapidly repaired by cells using one of two principal pathways that are conserved in plants and animals. In one pathway, the DNA ends produced by the break are re-joined by the cell's repair machinery in a sequence-independent manner (i.e. regardless of the sequence at each end). This is known as non-homologous end-joining (NHEJ). NHEJ does not necessarily restore the original sequence as it (and similar pathways) produces an insertion or deletion (an 'indel'), usually of a small number of nucleotides, in a way that cannot be controlled at present. The other major pathway, homology-directed repair (HDR), is DNA sequence dependent and uses an additional matching piece of DNA to provide template information that allows the double-strand break to be repaired correctly. HDR can also be used to add or remove a prescribed DNA sequence at the site of the double-strand break in a manner that can be controlled. The balance between the employment of NHEJ and HDR repair pathways by a cell in particular contexts is not well understood and is an active area of research.[16]

1.14 The role of ZFNs and TALENs is therefore to produce a targeted double-strand break in the genome, which the cellular machinery then repairs. The requirement for two engineered ZFN or TALEN proteins for every target is advantageous because it increases the specificity by decreasing the likelihood that the break will be made at an unintended point in the genome that has a similar sequence to the one the 'fingers' are designed to recognise (an 'off-target effect'). The disadvantage is that it requires considerable effort to design, synthesise and optimise a pair of proteins for every editing procedure.

CRISPR-Cas9

1.15 In 2012, it was discovered that a system of defence against viral attack found in the bacterium *Streptococcus pyogenes* could be adapted as a programmable system for genome editing.[17] The

[15] Skarnes WC (2015) Is mouse embryonic stem cell technology obsolete*? Genome Biology* **16**: 109.
[16] See, for example, Paquet D, Kwart D, Chen A, *et al*. (2016) Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9 *Nature* **533**(7601): 125-9.
[17] Jinek M, Chylinski K, Fonfara I, *et al*. (2012) A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity *Science* **337**(6096): 816-21.

system comprises two elements. The first is generically termed 'clustered regularly interspaced short palindromic repeat' (CRISPR) RNA; the second is 'CRISPR-associated protein 9' (Cas9), an endonuclease. The prototypical CRISPR components from S.*pyogenes* comprise two types of RNA molecule that scientists combined into one, called a single guide RNA (sgRNA) or guide RNA (gRNA).[18] In genome editing, sgRNA pairs with its predetermined genomic DNA target to form an heteroduplex (so-called because the RNA and DNA that pair together are different types of molecule). One region of the sgRNA matches with its exclusive DNA target site, giving the system specificity, while another region binds to the Cas9 protein. This guides the Cas9 to make a double-strand cut at the target site. Targeted, double-strand genome breaks made by sgRNA-Cas9 are repaired by the same ubiquitous NHEJ or HDR inbuilt cellular repair pathways operating for breaks made by ZFNs and TALENs. In 2013, the CRISPR-Cas9 system was shown to edit mammalian genomes with a high efficiency.[19]

1.16 CRISPR-Cas9 has several advantages when compared to its genome engineering forerunners. Its specificity to the target is secured by the way it exploits nucleic acid base-pairing – a feature that also underlies the fidelity of DNA replication and transcription in the animal and plant kingdoms (and consequently makes all DNA molecules, whatever their origin, amenable to editing in this way). It is so much more efficient (in terms of successes per attempt) that for the first time multiplex mammalian genome editing (editing several different genome sites in one procedure) has been achieved. The components are trivial to produce: sgRNA is only approximately one hundred nucleotides in length and can be synthesized with commercially available kits. The system functions with a universal Cas9 protein framework that dispenses with the need to design a different protein for each DNA target.

1.17 The comparatively short length of DNA coding for sgRNA-Cas9 renders it amenable to delivery by viruses, some of which are well-characterised in research and clinical contexts, but in which there are often strict limits on the size of additional inserted DNA that allow efficient virus assembly. Relatively short Cas9 species orthologues (Cas9s from different species that are different but perform a similar function), like the one from *Staphylococcus aureus*, help to meet size constraints, and others from *Neisseria meningitidis* and *Francisella novicida* (Cpf1) may offer distinctive advantages regarding size, target selection and target specificity. The current picture is one in which an already efficient system is undergoing continued refinement.

1.18 CRISPR-Cas9 works by causing a targeted DNA break but it is possible to replace the DNA cutting activity of Cas9 with other activities. For example, the DNA cutting activity can be replaced with DNA methylating or histone modifying activities. This means that an altered Cas9 (nuclease-dead Cas9) can, instead of making a double-strand break, perform an epigenetic modification at a prescribed site on the genome. This allows it to switch selected genes off or on without altering their sequence. Avoiding the need to alter genomic DNA sequences in this way may have advantages in contexts where the aim is to control gene expression without introducing heritable alterations to DNA.[20]

1.19 Given the rapidity of advances with CRISPR-Cas9, it is reasonable to ask what limitations it has and what it promises from a technical standpoint. One concern with the CRISPR-Cas9 system is the potential for off-target effects (editing at sites in the genome other than those intended). These concerns arose originally from analyses of editing in cell populations but single-cell analyses have subsequently suggested that these initial studies exaggerated the lack of specificity. Moreover, engineering of Cas9 protein and sgRNA frameworks have increased specificity further, so that

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[18] Ibid. The terms 'sgRNA' and 'gRNA' are often used synonymously and are used in all editing procedures. Accordingly, we will use sgRNA when referring to editing constructs, and to CRISPR-Cas9 when referring to the system generically.

[19] Cong L, Ann Ran F, Cox D, *et al*. (2013) Multiplex genome engineering using CRISPR/Cas systems *Science* **339**(6121): 819-23; Mali P, Yang L, Esvelt KM, *et al*. (2013) RNA-guided human genome engineering via Cas9 *Science* **339**(6121): 823-6.

[20] Thakore PI, Black JB, Hilton IB, *et al*. (2016) Editing the epigenome: technologies for programmable transcription and epigenetic modulation *Nature Methods* **13**(2):127-37.

now experiments have been performed in which no off-target cutting has been found, even when it is searched for by whole-genome sequence analysis.[21] Another complicating factor is that 'mosaicism' has been commonly observed in mice generated by the injection of CRISPR-Cas9 reagents into single-cell mouse zygotes. Mosaicism describes the situation in which not all cells of an individual are genetically identical but, instead, cells harbouring distinct mutations co-exist in the same organism. This implies such individuals may transmit several distinct mutations to the next generation. Strategies to reduce or eliminate mosaicism are being developed.[22]

1.20 So young a technology has, nevertheless, yet to be fully delineated. There may, for example, be classes of genomic DNA sequence that are refractory to CRISPR-Cas9. A very significant limitation to the practical deployment of the technique is the state of knowledge of gene function: CRISPR-Cas9 cannot be used to introduce or eliminate traits until its users know which regions of the genome to edit. Overcoming this obstacle requires considerable advances in the domain of genetics, although this is something to which genome editing can itself contribute as a powerful technique in laboratory research.[23] However, if genome editing is to prove practically valuable in the way that crop breeding, livestock domestication and biomedicine have done to date, it will be equally important, and arguably much more difficult, to demonstrate that the phenotypic modifications that may be achieved in the laboratory can be achieved in the field, the barn, and the clinic, and, equally importantly, to ensure that they can be introduced safely, ethically and acceptably in these contexts.

[21] 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)**:** 490-5; Slaymaker IM, Gao L, Zetsche B, *et al*. (2016) Rationally engineered Cas9 nucleases with improved specificity *Science* **351**(6268): 84-8.

[22] Singh P, Schimenti JC and Bolcun-Filas E (2015) A mouse geneticist's practical guide to CRISPR applications *Genetics* **199**(1): 1-15.

[23] Genome editing can, for example, relatively easily 'knock out' a gene of interest by introducing a mutation (indel) that would inactivate the gene, allowing researchers to make inferences about the gene function from subsequently observed differences in the modified organism. However, further research would be necessary to establish that an effect that is reproducible in experimental conditions is also reproducible outside those conditions (in a 'natural' or 'wild' environment).

Section 2

Science in context

Section 2 – Science in context

Overview

This section offers an account of the external conditions that bear on the production of knowledge and the development of technologies using genome editing. This is intended to complement the discussion in the previous section, which considered the nature of the techniques and emergence of the concept of genome editing within the context of the biological sciences. The present section therefore explores the interaction and interpenetration of science, and particular developments within science, and the wider society in which it takes place.

The vaunted advantages of genome editing, especially the CRISPR-Cas9 system, in terms of relative speed, accuracy, efficiency, low cost and ease of use are put into context, in relation to some of the current applications in basic research, such as the generation of gene-targeted mice. Current limitations in cases where new genetic elements or multiple edits are to be introduced, and where use is dependent on allied skills such as animal breeding, are described. Consequently, claims about the advantages of genome editing have to be considered carefully and in a broad context. Advances in genome editing may therefore reveal bottlenecks elsewhere that will impede the development of practical applications. External constraints on research, in terms of how research is encouraged and resourced, and the cultural responses of researchers to these factors have also influenced the attention given to genome editing.

The relationship between research and innovation is discussed. Although scientific research is thought to be socially beneficial, the relationship is complex and non-linear. Despite this, the idea of research impact is still considered by some to be an important rationale and justification for research funding. Another important expectation is that scientific knowledge should be available as a public good; this ethos is occasionally in tension with the reliance of innovation systems on private enterprise and has given rise to intellectual property rights (IPR) that secure the producer's income while allowing their know-how to be made publicly available. The commercial value of companies with IPR makes market speculation a factor capable of shaping innovation and concentrating power in the hands of certain firms, complicating the relationship between supporting research and securing societal benefits.

Consideration is given to the sense in which genome editing is transformative (capable of significantly changing practice and reorganising concepts). The implications that this transformative potential has for the broader public interest in the technology are discussed and the question is raised about the extent to which this interest reaches through into basic or underpinning research, and how that interest might be given effect through governance and regulation.

The significance of the 'editing' metaphor is examined and the need is noted for a coherent relationship between systems of concepts within science and within normative discourses by which they are governed, such as those of law and morality. The disruption of this relationship and the need to re-establish it in the case of transformative biotechnology is noted.

The conclusion identifies two main sources of public interest in genome editing, concerning societal investment in research and innovation and the potential impact of genome editing on the wellbeing and moral fabric of societies.

Introduction

2.1 Genome editing is primarily used in scientific research at present, where specialist knowledge and skill are brought to bear on the design and execution of experiments to produce, confirm or challenge ideas. The rapid adoption and diffusion of genome editing in the biological sciences, particularly the CRISPR-Cas9 system, has been due largely to its perceived superiority, in ways that are valued by users, to existing techniques, and to the fact that it enables experiments to be accomplished that were not previously achievable. Genome editing has, however, potentially many wider uses than as a scientific research technique.

2.2 In the Nuffield Council's 2012 report, *Emerging Biotechnologies: technology, choice and the public good*, biotechnologies were characterised as 'conjunctions of knowledge, practices, products and applications'.[24] This characterisation emphasises the way in which science and its practices, objects, conditions and aims correspond with and influence each other as biotechnologies emerge and become established in different fields of application. It offers a useful way of thinking about the prospects and possible pathways for genome editing. Having looked at the techniques of genome editing themselves in section 1, this section considers how these techniques might come

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

to comprise new treatments and technologies, and how such developments may be influenced by (and influence) a range of contextual conditions. These conditions include institutional, economic, social, legal and moral conditions that determine how quickly or slowly genome editing emerges, the objectives to which it is directed, the geography of its use, and the technological forms it takes.

Research and innovation

Basic research

2.3 Why has genome editing, particularly the CRISPR-Cas9 system, spread so rapidly through the biological sciences? The main advantage of CRISPR-Cas9 in comparison to previous methods is its versatility and ease of use. The availability of proprietary CRISPR-Cas9 kits requiring less technical skill (compared to ZFNs and TALENs) make genome editing, in effect, an off-the-shelf technology. This is made possible by the ease of production of both the CRISPR component, which is a short guide RNA (sgRNA), and Cas9, which is a one-size-fits-all protein that can be used to cut perhaps any DNA sequence. The use of synthetic guide RNA led to a widespread uptake in laboratories around the world as guide RNA is made to order and delivered by post.[25] Successful genome editing by CRISPR-Cas9 requires skills that can readily be acquired by those with standard degree level skills in molecular biology, which both potentially lowers the cost of deploying it (if it is no longer necessary to have expensively trained specialists) and increases the potential pool of users.[26] (This pool might potentially extend to include non-specialists and even amateur enthusiasts.)

2.4 The CRISPR-Cas9 system makes experiments that involve editing stem cell genomes *in vitro* quick to design and execute, allowing very rapid progress without expensive equipment and reagents. A final year undergraduate, for example, might feasibly design some sgRNAs and make a mutated cell line in a 10-week project. Furthermore, the *in vivo* use of CRISPR-Cas9 can imply significant time and cost savings in the generation of animal models through the direct injection of Cas9 and transcribed sgRNA into early embryos (zygotes). This is a more efficient way of producing the desired mutation, allowing the ES cell targeting phase to be bypassed, meaning that the generation time for rodent models can be reduced from over a year to just a few weeks, while the precision of editing is improving.[27] Moreover, mutant mice used for the study of disease can be produced in just one generation rather than after multiple generations of breeding, as was the case using previous methods that involved backcrossing modified mice through several generations to ensure the desired variation appeared in the desired inbred genetic background.

2.5 While the CRISPR-Cas9 system has enabled one-step generation of knockout mice by microinjection of zygotes, low success rates of introducing new functional DNA elements (cassette knock-in) in the same fashion currently limit its range of application, at least without recourse to embryonic stem cell approaches.[28] In fact, the efficiency of CRISPR-Cas9 varies considerably depending on the repair pathway (NHEJ or HDR, with HDR hitherto less efficient or not available in certain cases) and among cell types and organisms.[29] Furthermore, multiple edits may prove challenging in some circumstances owing not to the ineffectiveness of the editing system but to

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[25] See: Petherick A (2015) Outlook: genome editing *Nature* **528**(7580): S1.

[26] The ease of use of CRISPR-Cas9 has contributed significantly to the rising number of orders for genome-editing kits (for example from producer Addgene) for different genome editing applications from ca.2.500 in 2012 when CRISPR was introduced to more than 20.000 in 2014 and a growing number of research tool companies are launching CRISPR-related products. See: Baker M (2014) Gene editing at CRISPR speed *Nature Biotechnology* **32**(4): 309-12; Corbyn Z (2015) Biology's big hit *Nature* **528**(7580): S4-S5.

[27] Hsu PD, Lander ES, and Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering *Cell* **157**(6): 1262-78.

[28] See, however, Aida T, Chiyo K, Usami T, *et al*. (2015) Cloning-free CRISPR/Cas system facilitates functional cassette knock-in in mice *Genome Biology* **16**: 87.

[29] Golic KG (2013) RNA-guided nucleases: a new era for engineering the genomes of model and non-model organisms *Genetics* **195**(2): 303-08; Hsu PD, Lander ES, and Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering *Cell* **157**(6): 1262-78.

natural cellular repair mechanisms, which mean that if multiple double-stranded breaks are introduced into a single genome they may recombine with each other, in effect scrambling the genome. It may be possible, however, to circumvent such an outcome: as an alternative to introducing DNA breaks to effect editing, enzymatically modified forms of Cas9 have been produced to allow the targeted, direct conversion of one DNA base into another – so-called 'base editing'.[30] Moreover, performing multiple edits in a cell line context should permit selection of the appropriate cell genotype prior to further use. Culture of cells and micromanipulation of embryos, and their reintroduction to living animals, also require, variously, controlled laboratory conditions, precision equipment and advanced embryology and surgical skills.

2.6 Thus, while it is commonly and frequently claimed that genome editing has become significantly (perhaps radically) quicker, cheaper, more efficient, easier to use and therefore more accessible, care is needed when interpreting these claims.[31] The extent to which genome editing displays these features varies considerably, depending on many factors, including the field of application, the precise technique used, how it is applied and who is using it. Furthermore, although it greatly facilitates some research procedures, this will often reveal other bottlenecks and challenges confronting researchers. Nevertheless, the efficiency of genome editing, particularly CRISPR-based systems, is continually being improved.[32] We should therefore, at least for the purposes of this ethical discussion, take seriously the reality that it is already possible to make affordable and efficient edits to any genome with seemingly very low risk of unintended, direct molecular effects.

2.7 In addition to the intrinsic features of the technique, the rapid development and diffusion of genome editing techniques to date has been driven by both demand from researchers and high-profile advocacy by the developers and early adopters, and enabled by the conditions and culture of research in the biological sciences.[33] Biological research is international in scope, shares a domain of problems that transcend national interests, and communicates in a *lingua franca* (English), including through open access publication that allows universal diffusion and the formation of consensus. That culture, however, itself develops in response to a number of extrinsic influences and constraints.[34]

2.8 One of the main constraints on research is resources. In recent years, the direction of applied research has been significantly shaped by the interaction of several factors, often driven by the need to secure adequate funding. State funding is increasingly dependent on the demonstration of past success by research teams and on the articulation of a promise of future value.[35] Contemporary funding streams, such as those of the UK Research Councils and the European Union's Horizon 2020 programme, are orientated by 'societal challenges'.[36] In practice, while this may mean that research questions are addressed under different rubrics from the point of view of funding ('stem cell research' rather than 'developmental biology', for example) it may also mean

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30 Komor AC, Kim YB, Packer MS, *et al*. (2016) Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage *Nature* **533**(7603): 420-4.

31 This claim, particularly in respect of the CRISPR-Cas9 system, was found in many of the responses to our *Call for Evidence*, for example: PHG Foundation; Christian Medical Fellowship; MRC Harwell; Vlaams Instituut voor Biotechnologie (VIB); Carolyn Riley Chapman; Royal Society; Association of Medical Research Charities (AMRC); Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC); Angel Petropanagos, Dalhousie University and Carlos Mariscal, Dalhousie University & University of Nevada; Wellcome Trust.

32 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; Slaymaker IM, Gao L, Zetsche B, et al. (2016) Rationally engineered Cas9 nucleases with improved specificity *Science* **351**(6268): 84-8.

33 The promotion of CC9 has arguably transcended conventionally measured forms of communication of incremental scientific advance. It has been supported by charismatic and high-profile advocates (e.g. Jennifer Doudna, George Church), with the encouragement of commentators (e.g. Steven Pinker), vested interests (research funders and patent holders) and both the scientific and popular press. It appeals to scientists trying to stretch their exiguous grant money.

34 The unintended consequences of such constraints for scientific culture were discussed in *Emerging Biotechnologies* (see: http://nuffieldbioethics.org/project/emerging-biotechnologies/) and explored further in the Council's *Research Culture* engagement project (see: http://nuffieldbioethics.org/project/research-culture/).

35 The 'impact agenda' is one of a broader set of conditions that influence the phenomena of contemporary scientific research culture as their (sometimes unintended) effects. See *ibid*.

36 For Horizon 2020, see: https://ec.europa.eu/programmes/horizon2020/en/h2020-section/societal-challenges. There is inevitably some uncertainty associated with this given the result of the 2016 referendum on the UK withdrawing from the European Union.

a change in the kinds of research question that are addressed, as well as how researchers interact with those outside the laboratory, and how they explain, locate and portray their work in the world. Whereas scientific knowledge is international, science funding is often national, and researchers are constantly embroiled in direct competition for resources, jobs and recognition.[37]

2.9 Researchers who are not funded by the state may also need to account for the value of their work. For example, those employed in the commercial sector are likely to emphasise the value of their research in terms of enhanced shareholder value, while researchers funded by charitable foundations may be more inclined to emphasise the contribution of their research to the charity's strategic mission. Very little contemporary research is funded purely on the evaluation of past performance; most is funded on the basis of *projects*, that fall within particular strategic programme areas, in the expectation that transferable or commercially valuable knowledge will be produced.

Emerging technology and innovation

2.10 How the relationship between research and technological innovation is understood informs the formulation of research funding policy, and reveals or obscures opportunities for the ethical governance of science. A commonplace but now largely discredited perspective viewed science as a resource from which innovators draw, leading to new technological innovations that provide social or commercial benefits, such as increased wellbeing and productivity.[38] The flaws in this 'linear model' are generally thought to stem from its failure to give due attention to the complexity of innovation processes, the importance of feedbacks, the role of markets and other actors, and the effects of uncertainty and serendipity. Science now tends to be seen less the wellspring of technological innovation than a 'co-producer' along with these other forces and actors. Nevertheless, future applications of scientific research continue to have a justificatory role with regard to research in general and – increasingly, even – in particular, through the contemporary 'impact agenda' that pervades academic research evaluation and funding.[39] In private companies, future applications justify expenditure on research and development (although expenditure on *basic* research is left largely to the academic sector).[40]

2.11 Sociologists of science have long observed the dependence of science on particular types of social and institutional structures.[41] Writing in the early 1940s, the sociologist Robert Merton identified 'common ownership' as an integral element of the modern scientific ethos, in which the substantive findings of science are understood as a product of social collaboration and thus assigned to the community "as common heritage, in which the equity of the individual producer is severely limited."[42] The scientific ethos of common ownership also coheres with the nature of information and technological knowledge or know-how as a 'public good'. From an economic

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[37] On the perceived role of individuals, see George Church's counterblast to the lionisation of Jennifer Doudna (The Scientist (29 December 2015) *Credit for CRISPR: a conversation with George Church*, available at: http://www.the-scientist.com/?articles.view/articleNo/44919/title/Credit-for-CRISPR--A-Conversation-with-George-Church/) and the furore over Eric Lander's alternative hagiography in *Cell* (Lander ES The heroes of CRISPR *Cell* **164**(1): 18-28; The Scientist (19 January 2016) *"Heroes of CRISPR" disputed*, available at: http://www.the-scientist.com/?articles.view/articleNo/45119/title/-Heroes-of-CRISPR--Disputed/).

[38] The 'linear model' is conventionally traced to Vannevar Bush's influential 1945 report *Science, the endless frontier* (United States Government Printing Office, Washington), available at: https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm. See also Godin B (2006) The linear model of innovation: the historical construction of an analytical framework *Science, Technology & Human Values* **31**(6): 639-67 and Edgerton D (2004) The linear model' did not exist: reflections on the history and historiography of science and research in industry in the twentieth century, in *The science-industry nexus: history, policy, implications*, Grandin K, Wormbs N and Widmalm S (Editors) (Sagamore Beach, MA: Science History Publications), pp31-57.

[39] The different ways in which 'impact' figures in funding among the Higher Education Funding Councils and Research Councils are often poorly understood, at least outside academia. For RCs see: http://www.rcuk.ac.uk/innovation/impacts/.

[40] For a comparative assessment of UK gross domestic expenditure on research and development see, for example: http://www.publications.parliament.uk/pa/cm201516/cmselect/cmsctech/340/34006.htm.

[41] The canonical work is Merton R K (1973 [1942]) The normative structure of science, in *The sociology of science: theoretical and empirical investigations*, Storer NW (Editor) (Chicago and London: The University of Chicago Press), pp 267-78.

[42] Merton, op.cit., 273.

perspective, information (including the knowledge generated from scientific research) has two important characteristics: the consumption of information is both non-rivalrous (one person's use of information does not diminish any other person's ability to use the same information) and non-exclusive (once produced, information can be made available to all others at negligible additional cost).[43] The fact that it is easy to share information and difficult to exclude others from access to information once it is in circulation means that it is likely to be under-produced if provision is left to the interplay of the forces of demand and supply in the market (since 'free riders' who consume a good they have not shared in meeting the cost of producing, will undermine the producer's investment), yet there is no value-free mechanism for determining the appropriate level of provision.

2.12 The development of intellectual property regimes can be understood as a response to the problem of incentivising the provision of 'informational goods' such as scientific knowledge. In particular, the patent system essentially creates artificial property rights in order to spur innovation by creating a monopoly in favour of the patent-holder for a limited period of time and requiring the publication of know-how in return.[44] Hence the communal character of modern science was, even at the time when Merton was writing, fundamentally in tension with understandings of technological know-how as private property, which is given legal recognition within capitalist economic systems in the form of legally enforceable intellectual property rights.[45] Since the 1970s, the quest to secure patent rights has been influential in shaping the dynamics of research in the biosciences, spurred by the passage in the USA of the Bayh-Dole Act, which took effect in 1981, allowing US universities and small businesses to own patents in the inventions that they had developed with US federal government research funding.[46]

2.13 In the contemporary context, the need to secure funding and commercial investment through the promise of market exclusivity secured by intellectual property rights and stock market speculation on the value of biotechnology firms are likely to play a significant part in shaping the dynamics of scientific research and technological innovation. The reporting of the CRISPR-Cas9 system in the scientific press was attended by an increasingly high profile patent dispute between the two main claimants to intellectual property in the underlying invention.[47] Since then the prospects of biotechnology firms using genome editing are regularly analysed in the business press.[48] All of these factors may exert influence on the orientation of research and may, in turn, generate ethical concerns.

2.14 Critics of the patent law regime question the extent to which it strikes a balance between the private interest of patent owners and the overall social gains of the patent system,[49] with a growing consensus shared by economic historians and industrial organisation scholars that the importance of IP rights varies significantly across industries and fields of innovation, and that the link between

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43 Stiglitz JE (1999) Knowledge as a global public good, in *Global public goods. International cooperation in the 21st century*, Kaul I, Grunberg I and Stern MA (Editors) (New York: Oxford University Press), pp308-25.

44 Hettinger EC (1989) Justifying intellectual property *Philosophy and Public Affairs* **18**(1): 31-52.

45 Merton, op.cit, 275. These protections have certain relevant (although potentially difficult to interpret) limitations: for example, the EU Biotechnology Directive (Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:HTML) prohibits patenting of "processes for modifying the germ line genetic identity of human beings."

46 Drahos and Braithwaite comment that prior to the Bayh-Dole Act, "patents in such inventions ended up with the relevant federal funding agency, or the inventions were put straight into the public domain by means of publication. The enactment of Bayh-Dole resulted in "US universities and hospitals hurrying to the patent office. In the 5 years following Bayh-Dole these organizations increased their patent applications in the human biological area by 300 per cent." Drahos P and Braithwaite J (2002) *Information feudalism* (London and Sterling, VA: Earthscan Publications), at page 163.

47 Smith-Willis H and San Martín B (2015) Revolutionizing genome editing with CRISPR/Cas9: patent battles and human embryos *Cell and Gene Therapy Insights* **1**(2): 253-62.

48 See, for example: Forbes (31 May 2016) *Riding the gene editing wave: reflections on CRISPR/Cas 9's impressive trajectory*, available at: http://www.forbes.com/sites/brucebooth/2016/05/31/riding-the-gene-editing-wave-reflections-on-crisprs-impressive-trajectory/#2f1959fd141c.

49 See, for example, Picciotto S (2003) Private rights vs. public interests in the TRIPS agreement *Proceedings of the Annual Meeting (American Society of International Law)* **97**: 167-72.

IP rights and social welfare improvement is extraordinarily complex.[50] The existence of what appears to be a highly competitive market for biotechnology patents and the licensing regime that it has spawned suggests that IP rights do not, at present, constitute a major obstacle to the discovery phase of scientific research. However, the costs associated with the development, distribution and marketing of products that utilise these discoveries can, in practice, only be borne by the major corporate firms that operate in the biotechnology sector, with potential consequences for global development, access and distribution, and distributive justice.[51] (We will return to this in relation to particular fields of application in sections 4 to 7.)

Box 2.1: CRISPR-Cas9 patenting

The origins of the CRISPR-Cas9 system are a matter of controversy. Like almost all modern scientific discoveries, a large and interacting cast of characters is involved.[52] The patenting system nevertheless militates against the collaborative ethos by assigning rewards on the basis of priority, and is compounded by other rewards and accolades, including international science prizes (a Nobel prize is assumed to be at stake).

One US academic group (Feng Zhang at The Broad Institute at Harvard University and MIT) has been granted a US patent on CRISPR as a gene editing tool but another US academic group (Jennifer Doudna and Emanuelle Charpentier at the University of California, Berkeley) has a pending patent submission that predates the one already granted.[53] This has raised concerns that the IP will deter researchers from using CRISPR, and that the uncertainty of ownership will deter commercial companies. Through our interviews, and from the number of publications we found no evidence that either of these two concerns was justified.

It is likely that the patent landscape will become complex, and it may take years before the ownership of any particular claim becomes clear, probably only through litigation. Getting clarity could take 10-15 years, and the outcomes may be different in different jurisdictions, notably in the US compared to Europe. How, therefore, could this not become a major issue?

- It is generally accepted, at least outside the USA, that pre-commercial research is exempt from IP, in that it is not necessary to have a licence to explore the usefulness of the claims, and the IP owner is not expected to act to prevent such exploration in practice. It may also be in the IP holder's interest to have ongoing research that may expand the utility of their claims.
- CRISPR-Cas9 falls into the category of 'enabling technology', i.e. its use does not directly provide a product but it enables a product to be made using other knowledge and probably technology. Historically, this type of IP has been licensed through a 'fully paid-up licence', i.e. the IP holder does not share a royalty on any product resulting from its use, just one or a series of payments, which may be tiered depending on the scale or number of products. Only in rare cases does the IP holder refuse to licence, where they have their own applications to advance and where they use the IP to keep others out. Given the breadth of potential application and the fact that the main contenders for ownership are universities this is unlikely. It is usually in the interests of the IP owner to allow the widest use, to increase the chance that someone will find a valuable application, so that they can set the price higher than if it were set before any solid uses had been identified. A similar situation prevailed with IP covering the polymerase chain reaction (PCR) technology that underpins genetic research and genome sequencing: progress was not hindered and, when a kit is sold by a laboratory supplier, it includes a small payment for the right to use the IP, which is invisible to the user.
- Many commercial companies have already taken a licence from one or both of the patent contenders, either because they have a view on who will ultimately win, or because they believe the licence will be less expensive while uncertainty remains.
- In addition to the broad claims, the specific Cas9 claims and, potentially, claims on modified CRISPR components, two other pieces of IP are likely. The first is a claim that identifies how to address a specific application (e.g. editing such and such allele would control such and such disease) and, very likely, a narrower claim for a specific method that efficiently and effectively results in a product that delivers the potential benefit. There could therefore be at least four levels of IP that would need to be assembled to gain freedom-to-operate on any specific invention. This has raised concerns about the potential for 'evergreening' patents (to extend exclusivity)[54]; past experience, however, suggests

[50] Mennell PS (2000) Intellectual property: general theories, in *Encyclopedia of Law & Economics: Volume II*, Bouckaert B and de Geest G (Editors) (Cheltenham: Edward Elgar), pp129-88.

[51] Drahos P and Braithwaite J (2002) *Information feudalism* (London and Sterling, VA: Earthscan Publications), at page 166.

[52] Lander ES (2016) The heroes of CRISPR *Cell* **164**(1): 18-28; Ledford H (2016) The unsung heroes of CRISPR *Nature* **535**(7612): 342-4.

[53] Smith-Willis H and San Martín B (2015) Revolutionizing genome editing with CRISPR/Cas9: patent battles and human embryos *Cell and Gene Therapy Insights* **1**(2): 253-62.

[54] 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/.

> that although this process can extend patent life, it does so only on an increasingly narrow base, as the initial, broader patents expire.

2.15 The factors that act to attract, secure and consolidate investment may also have the effect of confirming a course for innovation, creating both 'lock in' of contingent technological forms and forward momentum along a particular technological pathway.[55] The reasons for this include factors such as sunk costs, learning effects, increasing returns to scale, high transaction costs associated with any change of direction and the mutual adaptation between technologies and associated conditions of use, including the structure, governance and practice of institutions, and not excluding social conditions, normative rules and standards,[56] and public acceptance.[57] This is not to deny that commitment to a particular course may have associated benefits (for example, efficiency, economies of scale) but it is important to recognise that different bundles of benefits and costs (including unforeseen and unintended consequences, both deleterious and serendipitous) may be defined and valued differently from different societal perspectives.

Is CRISPR-Cas9 a transformative biotechnology?

2.16 Questions of how the technologies emerge and are adopted may lack much broader public significance so long as genome editing, or particular systems such as CRISPR-Cas9, remain merely techniques among others, at the disposal of scientists for the execution of particular tasks. They become significant, however, if the technologies that they underpin become so dominant that they overtake and potentially transform an area of practice.[58] Economic analysts refer to such technologies as radical innovations or 'disruptive technologies', although the 'disruption' may extend to social, institutional and moral domains as well.[59] Such technologies may have the capacity "to transform or displace existing social relations, practices and modes of production, or create new capabilities and opportunities that did not previously exist, or may not even have been imagined [in ways that] might be entirely unexpected or unsought."[60] An example of such a technology outside biology is semiconductor-based technologies, which replaced vacuum tubes and paved the way for the miniaturisation and commensurately increasing power of electronic computing. In biomedicine we might recall here that, in the 1950s, it was projected that the cost of treatment for those affected by poliovirus would absorb a huge percentage of the US healthcare budget; by the early 1960s, with effective polio vaccination, the cost of polio healthcare had

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55 On 'technological momentum' see: Hughes TP (1969) Technological momentum in history: hydrogenation in Germany 1898-1933 *Past and Present* **44**(1): 106-32; on 'lock in' see: Boas TC (2007) Conceptualizing continuity and change: the composite-standard model of path dependence *Journal of Theoretical Politics* **19**(1): 33-54.

56 In some cases, early market entrants can establish industry standard practice, which may become adopted into regulatory measures which then act as barriers to entry to the market for new firms, and consolidating the market dominance of the established firms. There is a stark disjunction in the so-called 'politics of regulation' between two perspectives: so-called 'public interest perspectives' understand regulation as created to serve the public interest (primarily in safeguarding society against various forms of harm, including market failure and other kinds of non-market risks); 'private interest' theorists (including public choice theorists), in contrast, emphasise the play of power involved in the establishment of regulatory standards and regimes, arguing that the most powerful players in the industry lobby politicians in order to secure regulatory norms that operate to further the interests of the industry (at the expense of the general public), often creating barriers to new entry and shoring up existing monopolies. In this way innovation trajectories may be shaped by political-economic forces that may not best serve the public interest, which is a source of ethical concern.

57 See: Winner L (1978) *Autonomous technology: technics-out-of-control as a theme in political thought* (Cambridge, MA and London: MIT Press). See also: 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) for the claim that the larger and more complex technological systems become, the more they tend to shape society and the less amenable they are to being shaped by it.

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

59 See: Christensen CM (1997) *The innovator's dilemma*: *when new technologies cause great firms to fail* (Boston MA: Harvard Business School Press) where a dichotomy is established between sustaining and disruptive technologies. It is of note that disruptive innovations often perform poorly at the outset, but survive and flourish due to adoption by a user group who find value in a feature that is not shared by incumbent technologies and may not be what is generally thought most valuable about that technology.

60 See Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, at page 40.

dropped precipitately.[61] Given the rapid diffusion of genome editing across biological research and its displacement of incumbent approaches, the impact of the CRISPR-Cas9 system and its analogues is potentially of this order and has already been compared to the invention of the PCR (polymerase chain reaction) method of DNA amplification that supports modern genetic testing, molecular cloning and genome sequencing.[62]

2.17 Nevertheless emerging technologies, which are promissory by nature, are characteristically subject to 'hype' and over-claiming.[63] Whether unintentional or deliberate, the structuring of expectations through the way in which the prospects of the technology are presented may help to create the conditions in which they are realised (for example by attracting funding or investment, identifying demand or stimulating prospective policy debates). It may, equally, crowd out alternative approaches, starving them of attention, favour or resources. Possibly adverse consequences of over-claiming in areas in which science encounters politics are increasingly recognised by the scientific community, and have led to renewed injunctions to present developments in research candidly and soberly, despite the competitive environment in academia as well as business.[64] Nevertheless, the formation of expectations and the interrogation, comparison or – in some cases – confrontation of different visions of desirable and scientifically attainable futures ('imaginaries') is vital to innovation.[65] It is not necessary (or possible) that this should take place in neutral language or against a background of acknowledged priorities and values; what is dangerous is where there are asymmetries of power, information or representation in the public sphere that mean that certain visions and values go unappreciated and others go unchallenged.[66]

Interpretation and governance

The metaphor of genome editing

2.18 Whether intentionally or not, the 'editing' metaphor distinguishes the approach from less 'precise' forms of genetic 'engineering' and, simultaneously, distances it from their associated connotations, including the range of public responses that these terms typically excite.[67] The editing metaphor also plays on characterisations of the genome as the 'book of life' containing 'sentences' (genes) made up of a 'genetic alphabet' of four 'letters' (A, C, G and T, the initial letters of the four chemical bases comprising DNA) that were common around the time of the Human Genome Project. [68] The editing metaphor transfers easily to the more contemporary image of

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61 Thompson KM and Duintjer Tebbens RJ (2006) Retrospective cost-effectiveness analyses for polio vaccination in the United States *Risk Analysis* **26**(6): 1423-40.

62 See Ledford H (2015) CRISPR, the disruptor *Nature* **522**(7554): 20-4.

63 "Emerging biotechnologies are promissory by nature. Belief in the beneficial prospects of a particular biotechnological initiative is necessary, but not sufficient, to bring that technology about; on the other hand, scepticism about those prospects may be sufficient, but not necessary, to cause it to fail." Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, at page 33.

64 See, for example, a recent update to guidelines from the International Society for Stem Cell Research, available at: http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2; see also: Caulfield T, Sipp D, Murry CE, Daley GQ and Kimmelman J (2016) Confronting stem cell hype: against hyperbole, distortion, and overselling *Science* **352**(6287):776-7.

65 See for example, Harvard Kennedy School of Government's 'Sociotechnical Imaginaries Project' (http://sts.hks.harvard.edu/research/platforms/imaginaries/) which explains the role of imagined future states as both aims and justifications for government policy initiatives.

66 See Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, Chapter 4 ('Public ethics and the governance of emerging biotechnologies').

67 References to genome editing's alleged 'precision' is challenged by some, pointing to the use of 'precision' as a 'thick' concept, connoting approbation (one that surfaces in a number of contemporary tropes, such as 'precision medicine' or 'precision warfare') or dissembling the actual capacities of the technology (confusing the ability to manipulate nucleotide sequence with precision with the level of control over the consequences of doing so in terms of gene function).

68 See, for example, a series of blogs by Brigitte Nerlich of Nottingham University, e.g.: *The book of life: reading, writing and editing* (22 November 2015): http://blogs.nottingham.ac.uk/makingsciencepublic/2015/11/22/the-book-of-life-reading-writing-and-editing/.

modifying computer code.[69] The metaphor suggests not only the type but also the significance of the intervention: it is technical, is not dependent on scale (as it applies equally to changes large or small) and is seen as corrective or improving (at least in relation to the editor's vision). In this way, the concept of editing has a certain thickness, whereby, while apparently descriptive, it implies a tacit evaluative judgement.[70] It also implies an editor (the one who does the editing) and, by deeper implication, may distinguish the editor, who merely corrects and improves, from a putative, creative 'author'. But whether authorship is assigned to a divinity or not, the implication is that the work of editing is trivial in comparison. (Genome 'rewriting', another trope in the extended metaphor that has been used, although less frequently, for this practice, suggests a more substantial intervention.[71])

2.19 Other metaphors have been used less commonly to describe the practice of genome editing. These include 'genome surgery' (which evokes the cutting and removal of sections of DNA as well as the typically medical aims of the practice) or genome editing as a 'magic bullet' (that eliminates undesirable genetic features without collateral damage or adverse consequences). It appears, however, that the metaphor of the genome-as-text has taken an unshakeable hold. This may owe something to its familiarity, its fertility and the apparent ease with which the metaphor may be extended. The danger of the metaphor lies not in the fact that it is a metaphor, and therefore a non-reducible way of referring to complex realities; it lies in the possibility that the metaphor might either dissemble significant ethical questions through the use of euphemism, or lead reasoning astray by overstretching the power of analogy.

Genome editing in law, regulation and morality

2.20 The existence of regulatory regimes and standards that are specifically concerned with biotechnology suggests that, rightly or wrongly, they are framed in legal and regulatory terms as having special societal significance. Such measures rely on decisions about what features of a biotechnology or product are to be treated as relevant and on the possibility of distinguishing (often using specific criteria) between different classes in order to subject them to different kinds of response. Thus, the regulatory regime for assisted human reproduction in the UK uses a variety of criteria (the kinds of activities carried out, the purposes at which they aim, the type of cells involved, etc.) to distinguish what is impermissible, generally permissible, or to be permitted only under licence.[72] In notable cases, such as that of somatic cell nuclear transfer (or, more thickly, 'cloning') the correspondence between, on the one hand, how these terms are constructed and interrelated as concepts employed within legal and moral systems, and, on the other, what contemporary genomics and embryology afford in practice can come to be tested.[73] In another example, genome editing is currently testing the approach to the legal regulation of genetically modified organisms in the European Union, not only with regard to whether genome edited organisms fall under the GMO legislation, but by precipitating a more fundamental reflection on the legislative approach and its moral and political foundations (to be discussed in section 5 below).[74]

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[69] See also: Merriman B (2015) "Editing": a productive metaphor for regulating CRISPR *The American Journal of Bioethics* **15**(12): 62-4.

[70] For 'thick concepts', see Bernard Williams (2006 [1985]) *Ethics and the limits of philosophy* (London and New York: Routledge).

[71] The notion of genome 'writing' has recently become associated with a project in synthetic biology to engineer whole human genomes, known as 'HGP-write' (see http://engineeringbiologycenter.org/), which has re-envisioned the original Human Genome Project, substantially completed in 2003, as 'HGP-read'.

[72] Leather S and Mills P (2005) Regulation of assisted reproductive technology: the UK experience – themes and trends, in *Textbook of in vitro fertilization and assisted reproduction*, 3rd Edition, Brinsden PR (Editor) (London: Taylor and Francis), pp623-31.

[73] In a judicial review that concerned whether embryos created by somatic cell nuclear transfer should fall under the regulatory regime of the UK's Human Fertilisation and Embryology Act 1990, the court was obliged to adopt a 'purposive' construction with regard to the meaning of 'embryo' in the 1990 Act (*R. v. Secretary of State for Health ex p. Quintavalle (on behalf of Pro-Life Alliance)* [2003] UKHL 13. A similar anxiety resurfaced in the case of 'human admixed embryos' which was settled by the Human Fertilisation and Embryology Act 2008.

[74] See, for example: Ammann K (2014) Genomic misconception: a fresh look at the biosafety of transgenic and conventional crops. A plea for a process agnostic regulation *New Biotechnology* **31**(1): 1-17; Kokotovich A and Kuzma J (2014) Conflicting

Conclusion: the public interest in genome editing

2.21 There is a public interest in research for at least two main reasons. The first is to the extent that a great deal of research in the academic sector is publicly funded, from money collected through general taxation. This implies a public interest in the fact that this money is spent in a way that reflects public priorities and pursues them with the greatest possible efficiency.[75] The second, more profound, reason is that products and practices, processes and tools produced by the application of knowledge gained through research may have a direct or indirect impact on the wellbeing and welfare of the public (including their moral and social welfare). The public have an *interest* in science, in terms of its expectation of net social benefits, and *invests* in science both financially and through the trust placed in scientists to contribute to the delivery of these benefits. But more profoundly than this, the public have an underlying public interest in the overall moral and ethical texture of the society in which they live. How technologies like genome editing are taken up and regulated both reflects and influences the broader moral values on which common social life is based and the social meaning of the practices in question.

2.22 Research and innovation in biotechnology and biomedicine are now contested intensely in political arenas, demanding both democratic engagement and attention to broader questions of justice and value:

> "technology, once seen as the preserve of dispassionate engineers committed to the unambiguous betterment of life, now has become a feverishly contested space in which human societies are waging bitter political battles over competing visions of the good and the authority to define it. In the process, the virtually automatic coupling of technology with progress, a legacy of the Enlightenment, has come undone. Uncertainty prevails, both about who governs technology and for whose benefit. No matter which way one looks, the frontiers of technology are seen to be at one and the same time, frontiers of politics."[76]

2.23 It is important but open to question whether, and the extent to which, this second reason – that research is not separate from but a part of social behaviour – reaches through into so-called 'basic' or 'underpinning' research, which is concerned with the production of knowledge without an immediate practical application in view. That is, regardless of the entitlement that funding secures, the extent to which basic research is bound up with the flux of social transformation or is itself part of the set of wider social practices. To the extent that it is part of the set of wider social practices, there is a public interest in the conduct (that it should proceed according to principles of moral behaviour, for example) and aims of research (for example, that it should endeavour to conform and contribute to the overall public good).

2.24 A difficulty in securing the optimum mix of public benefits and the avoidance of societal harm arising from research (alongside whatever private benefits are appropriate to the developers) arises from complexity and indeterminacy in the relationship between research and innovation. This makes the processes of biomedical and biotechnological innovation highly uncertain.[77] Whereas it is a reliable inference that the pursuit of scientific knowledge *in general* will contribute to more powerful technologies that can, in turn, give rise to productivity and welfare benefits (but may also have a greater capacity for harms if misused) it is not possible to conclude from this that the pursuit of any *particular* knowledge will do so. Nor is it possible to conclude that any given

futures: environmental regulation of plant targeted genetic modification *Bulletin of Science, Technology & Society* **34**(3/4): 108-20; Araki M and Ishii T (2015) Towards social acceptance of plant breeding by genome editing *Trends in Plant Science* **20**(3): 145-9; Conko G, Kershen DL, Miller H and Parrott WA (2016) A risk-based approach to the regulation of genetically engineered organisms *Nature Biotechnology* **34**(5): 493-503.

[75] This is particularly the case given the withdrawal of commercial firms from basic research owing to the financial risk involved, which they leave to be borne by the academic sector; on the other hand, in more recent years, there has been an increasing expectation that the academic sector will operate more like a business and secure IPR so it can commercialise its discoveries.

[76] Jasanoff S (2006) Technology as a site and object of politics, in *The Oxford handbook of contextual political analysis*, Goodin RE and Tilley C (Editors) (Oxford: Oxford University Press), pp745-63.

[77] For a discussion of uncertainty in relation to emerging biotechnologies, see Nuffield Council on Bioethics (2012) *op.cit.*

innovation will benefit all equally, or that it will not benefit some only at the expense of others, in ways that, regardless of net overall benefit, may be offensive to principles of justice. How the production of knowledge and innovation is managed, controlled and directed can therefore have potentially profound implications for the public interest.

2.25 In the second part of our programme of work on genome editing we intend to start with a domain of problems rather than with a particular technical development, in order to evaluate what impact genome editing may and should have, in order to consider both the value and opportunity costs of particular solutions, and to avoid hypothecating a particular set of societal challenges to a given technology. For the time being, however, having now considered the 'instances' of genome editing and the external circumstances of its emergence, we will continue to examine the moral perspectives from which it can be viewed and the chief questions to which it gives rise; that is, not genome editing itself but its moral, legal and social, and scientific and technological ramifications.

Section 3

Moral perspectives

Section 3 – Moral perspectives

Overview

This section elaborates some of the perspectives and concerns that inform moral responses to genome editing. A starting point is the assumption that the object of modern science is the improvement of the human condition. The uncertainty of this outcome, the freedom of inquiry this entails, and the potential for scientific knowledge to support adverse as well as beneficial outcomes requires public trust in scientists and enjoins scientists in a corresponding responsibility towards society.

The question of whether intervening in the genome is of particular ethical significance is considered and the respects in which it differs from other interventions are discussed. The question of distinctive responsibilities falling on genome scientists and the relevance of how these have been addressed in the past (notably the Asilomar conference on recombinant DNA technology) is also discussed.

Transformative developments in bioscience are shown to exert pressure on established moral norms. Conservative responses arising from moral intuition, precaution, resistance to perceived technological determinism and the virtue of established order are distinguished. Attempts to constrain expanded uses of biotechnology in relation to discovered norms of biological form and functioning, and by how those uses conform with human rights are discussed, as are the advantages and challenges of using decision rules based on calculations of predicted gains or reductions in welfare. Questions of social, global and intergenerational justice are raised and the significance of how questions about the appropriate use of genome technologies are answered for the moral fabric of societies is noted.

The need to resolve questions of the governance of genome technologies at a public level in plural societies is noted and the importance of having an effective public sphere is suggested.

Introduction

3.1 This section will identify some of the key moral perspectives on genome editing, derived from our *Call for Evidence*, fact-finding meetings and research interviews, and our review of the relevant literature.[78] Because these are extracted empirically from expressed statements, the presentation of these positions does not represent a comprehensive ethical analysis. Nor does it follow a necessary sequence, since one perspective does not entail another: they represent alternative views, which may be found together in practice and reconciled, sometimes with difficulty, in public statements of opinion or policy. The purpose here is to uncover the grounds of moral reasoning that are currently in play in the discourse around genome editing and to distinguish different sources for *normative* claims about genome editing. Some of the arguments informed by these perspectives will be considered in subsequent sections, and particularly in the second part of our work programme.[79]

Science as a moral enterprise

3.2 From the beginning of modern science, the pursuit of scientific knowledge was connected with the idea of moral purpose. In the *Advancement of learning*, Francis Bacon famously counselled against the 'greatest error of all', being to mistake the 'furthest end of knowledge' for anything other than "the glory of the Creator and the relief of man's estate".[80] The Charter of the Royal Society, the UK's national academy of science, likewise (or accordingly) refers to the President, Council and Fellows and their successors "whose studies are to be applied to further promoting

[78] See Appendix 1 ('Method of Working').

[79] Normative statements are of an evaluative or prescriptive kind; they are distinguished from statements that purport simply to describe or explain certain facts about the world, without expressing any disposition towards them. Norms that guide or constrain human behaviour may take different forms, for example in national laws or moral conventions. In the second part of our programme of work on genome editing, we will examine and develop arguments leading to normative claims about specific uses of genome editing that this 'platform' report has identified.

[80] Bacon, F (2000 [1605]) *The Oxford Francis Bacon, Vol. 4: the advancement of learning*, Kiernan M (Editor) (Oxford: Oxford University). By 'the relief of man's estate' Bacon meant the alleviation of the sufferings afflicting mortal life.

by the authority of experiments the sciences of natural things and of useful arts, to the glory of God the Creator, and the advantage of the human race."[81] Whereas knowledge is seen as instrumental, it is an instrument with an inherent purpose; the pursuit of knowledge for other ends, such as vanity or self-enrichment, is seen as a moral failing.

3.3 In contemporary discourse on science, an emphasis on liberal and meritocratic concepts of scientific freedom and excellence is more likely to be found than statements of essential moral purpose: for example, the *Universal ethical code for scientists* places emphasis on the implicit contract between science and society, which makes scientific freedom conditional on doing no harm (rather than actually doing good).[82] In reality the motivations and aims of scientists are likely to be more complex. Nevertheless, recent research by the Nuffield Council on Bioethics found that more working scientists put 'making scientific discoveries for the benefit of society' as their primary motivation for involvement in science than any other reason.[83] Irrespective of the intentions of scientists, it is hard to argue that that the pursuit of science, particularly in the modern period, has not had a transformative benefit to 'the advantage of the human race'. Nevertheless, the consequences of particular developments in knowledge are uncertain, and depend greatly on how they are put to use, wittingly or otherwise. As Bacon also noted, the mechanical arts are of ambiguous use, "and serve as well for the cure as for the hurt."[84]

3.4 The potential good of science and the implicit good will of scientists to avoid harm, in the context of an uncertain relationship between the scientific enterprise and its practical outcomes, is recognised in a common trope in social studies of science: the notional loan of trust or social 'licence to practise' given to scientists by society.[85] The relation between scientific inquiry and the broader public interest is also invoked to defend scientific inquiry against interference from commercial and political interests.[86] In return for these freedoms scientists are assumed to have an implicit responsibility towards society.[87] The degree of public trust and corresponding licence is, nevertheless, balanced between ambition and concern, and is sensitive to events and to narratives that celebrate the achievements of science, on the one hand, or draw attention to its failures, limitations and historical perversions, on the other.[88]

Intervening in the genome

3.5 In our *Call for Evidence* we posed the question of whether or not there was anything special about the genome that might make intervening directly in the genome different from other ways of manipulating nature (e.g. selective breeding of plants or animals). Responses to this question mostly highlighted the ways in which intervening in the genome is different in virtue of its role in

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81 See: https://royalsociety.org/about-us/governance/charters/. The formulation is found in the second charter of 1663 (and expands slightly on the reference to the 'useful arts' in the first charter of a year earlier.

82 This *Code* (2007), developed and promoted by the UK Government's former Chief Scientific Advisor, Sir David King, is not binding, but is widely referenced. It is introduced by a quotation from Sir David: "Our social licence to operate as scientists needs to be founded on a continually renewed relationship of trust between scientists and society." See: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/283157/universal-ethical-code-scientists.pdf.

83 In a 2014 online survey of working scientists (n=790), 35% of respondents chose 'making scientific discoveries for the benefit of society' as the first response to the question 'What motivates you in your work as a scientist?', above 'improving my knowledge and understanding' (29%).
See: http://nuffieldbioethics.org/wp-content/uploads/The_culture_of_scientific_research_survey_analysis_for_web.pdf.

84 Bacon F (1857) *Of the wisdom of the ancients*, available at: http://www.bartleby.com/82/19.html.

85 Surveys and studies suggest that this is less about specific technologies or scientific advances but, rather, about the more general goals of science and its applications. See, for example, *Eurobarometer Responsible research and innovation, science and technology* (2013): http://ec.europa.eu/public_opinion/archives/ebs/ebs_401_en.pdf; for a US perspective, see: Nisbet M and Markowitz EM (2014) Understanding public opinion in debates over biomedical research: looking beyond political partisanship to focus on beliefs about science and society *PLoS ONE* **9**: e88473. On 'social licence to practise', see Dixon-Woods M and Ashcroft RE (2008) Regulation and the social licence for medical research *Medicine, Health Care and Philosophy* **11**(4): 381-91.

86 See *Who owns science? The Manchester manifesto* (2009), available at: http://www.isei.manchester.ac.uk/TheManchesterManifesto.pdf.

87 The *Universal ethical code for scientists* recognises the responsibility corresponding to the 'social licence to practise' as one of its three cardinal principles.

88 On the negotiation between scientific and ethical orientations in the context of continuing research, see: Thompson C (2013) *Good science: the ethical choreography of stem cell research* (Cambridge, MA: MIT Press).

inheritance and the potential scale, seriousness and unpredictability of effects. However, there was little to suggest that the genome itself was an object of special reverence. We also posed a related question about whether any special responsibilities should fall on genome scientists, a suggestion that was, for the most part, robustly rejected: it was widely asserted that scientists had a responsibility to be open and candid about their work but these were felt to be responsibilities for *all* scientists, not peculiar to genome scientists, especially if the implication were that other scientists should be held to less exacting standards.

3.6 Intuitions about the significance of modification at a genomic level, as opposed to the modification of any other feature of an organism, are reflected in the various legal and regulatory provisions that apply to plants and animals (rules concerning GMOs in the environment and marketed for human consumption), and humans (gene therapy, assisted reproduction), as well as enhanced biosafety requirements for research. Concerns about the uncertain consequences of genome modification and the responsibilities of scientists to guard against them have long attended DNA research. They were the subject of a conference in 1975 that has become a point of reference for contemporary discussions about genome editing.

Box 3.1: The 1975 Asilomar Conference on Recombinant DNA

The conference on recombinant DNA held at the Asilomar Conference Grounds on the Monterey Peninsula, California, in February 1975 is often referred to as an important moment in the development of public responsibility within the science community.

The conference followed the raising of concerns about the potential safety hazards of (then) novel recombinant DNA technology, which allowed the combination of sections of DNA from different organisms and their insertion into a living host cell that was capable of propagating. The principal fear was that such experiments might give rise to new pathogens that could infect humans. At the instigation of researchers in the field, the US National Academies of Science (NAS) established a committee, which promptly called for a moratorium on recombinant DNA research pending an international conference to establish standards for research and regulation of biotechnologies.

The 1975 conference drew together the majority of the leading recombinant DNA researchers along with lawyers and medics, and its proceedings were placed in the public domain to encourage public discussion of research policy. As such it represents, for many, an important moment in wider public engagement with science policy in the recognition of the social importance of science and the social responsibility of scientists. (The December 2016 International Summit on Genome Editing, held in Washington, DC, under the auspices of the NAS, the UK's Royal Society and the Chinese Academy of Sciences was widely compared to the earlier Asilomar conference.)

The significance of the Asilomar conference is nevertheless disputed. Some consider it a lost opportunity or even a well-orchestrated subterfuge to allow research to progress with the minimum of external interference.[89] Its relevance to contemporary questions about genome editing has also been questioned, given that the scientific community concerned in the present case is large, diverse and globally diffused, that the issues are no longer about biosafety (about which reasonable scientific consensus is possible and which have, arguably, been settled) but rather about socially acceptable uses of the technology.[90]

Responses to the challenge to established norms

3.7 In section 2 it was suggested that genome editing is a potentially transformative technology, not merely in an economic sense but also in a moral sense, in that it has the capacity both to produce new differences in the world and to provoke new ways of thinking about differences in the world. There is a need for normative judgements to respond to the world as it is presented in the current state of scientific understanding. The requirement to formulate public policy, which was discussed in section 2, therefore enjoins an effort to produce a working correspondence between scientific and normative discourses, so that they do not simply 'talk past' one another. There are numerous historical examples of where this correspondence has failed and had to be shored up or remade.[91]

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[89] For a discussion of the relevance of the Asilomar comparison, see: 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/.

[90] Sarewitz D (2015) Science can't solve it *Nature* **522**(7557): 413-4.

[91] See Baylis F and Krahn T (2009) The trouble with embryos *Science Studies* **22**(2): 31-54. The applicability of UK human embryology legislation to embryos created by somatic cell nuclear transfer ('cloning') was challenged in *R. v. Secretary of*

A notable feature of genome editing, also discussed in section 2, is the rapidity with which it has been adopted as an experimental technique and with which the production of research findings and the development of biotechnologies are progressing on several fronts. These new findings and new capacities are inevitably putting pressure on the normative judgements enshrined in moral and legal codes, by spelling out possibilities that lie beyond the boundaries established in such codes and projecting plausible pathways by which they might be reached. Put together, emerging tensions in the correspondence between scientific understanding and social and moral norms, and the difference in relative pace of development raise the stakes for attempts to find a coherent public response at an appropriate level.

Bioconservatism

3.8 One response to such developments may be characterised as moral conservatism or, as it has been called in this connection, 'bioconservatism'.[92] This is often framed through a morally invested opposition between the 'natural' and technological.[93] Broadly conservative responses can be a matter of taste, or linked with an (innate or conditioned) emotional reaction (what the US commentator, Leon Kass, memorably characterised as the 'wisdom of repugnance'[94]); they can, equally, embody a response to the perceived threat of technological determinism (in the sense of modern technologies shaping and regulating human capacities and actions).[95] Bioconservatism may arise from a reasonable concern about scientific hubris (for which a fictional apotheosis is Mary Shelley's character, Victor Frankenstein[96]), which is sceptical about the wisdom of human agents disrupting finely balanced systems that have reached their present state through lengthy evolutionary processes. For some it may have roots in their religious faith.[97] Whether this providence is thought to be divine or natural, human interference beyond a certain point may be thought to overreach the limited cognitive capacities of human agents and the limits of predictability for the systems in question.[98] Bioconservatism might refer to social, as well as natural, adaptation, appearing as a response to science moving too quickly for processes of public moral reflection to keep pace. Here, the idea is of a system of generalised judgements constituting a well-established system, instantiated in moral norms, cultural practices, regulatory codes and legal instruments, which has demonstrated its advantages and cultivated reliance on it among those it has served.

Normality, moral norms and rights

3.9 For many there are positive reasons to extend the use of new genomic technologies beyond the limits of existing practices, while remaining within some bounds of acceptability in order to avoid the putatively undesirable moral and social consequences of anomie. A way of grounding the

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State for Health ex p. Quintavalle (on behalf of Pro-Life Alliance) [2003] UKHL 13 and later put beyond doubt by the Human Reproductive Cloning Act 2003; a similar concern related to human-animal hybrid or 'admixed' embryos (later provided for in the Human Fertilisation and Embryology Act 2008).

92 Although few authors self-identify as bioconservatives, the term is in currency in the bioethics literature. It transcends the political right and left, embracing those concerned about the effect of biotechnology on traditional values and ways of life and on social justice and equality.

93 See evidence supporting the Nuffield Council's 2015 work on *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/.

94 See: Kass LR (1998) The wisdom of repugnance: why we should ban the cloning of humans *Valparaiso University Law Review* **32**(2): 679-705, first published as Kass, LR (1997) The wisdom of repugnance *The New Republic* (June 2, 1997): 17-26.

95 See: Heidegger M (1977 [1954]) The question concerning technology, in *The question concerning technology and other essays*, Lovitt W (Translator) (New York and London: Garland Publishing), pp 3-35.

96 Shelley, M (1992 [1818]) *Frankenstein; or, the modern Prometheus* (London: Penguin Books).

97 This seems more marked in the case of individuals than in the official positions of faith organisations, and in the US than the UK. As part of our information gathering we consulted representatives from the Church of England, the office of the Chief Rabbi, from the Hindu Council UK, and the Sikh Missionary Society UK and the Muslim Council of Britain, as well as various Christian professional groups and NGOs. Despite differences of principle, which led them to place different conditions on the potential uses of genome editing, none was inherently opposed to genome editing in itself.

98 Many of those who share conservative conclusions with regard to biotechnology may hold them for principled and socially progressive reasons, for example in view of their implications for human rights (see para. 3.9 below).

distinction between acceptable and unacceptable interventions is offered by the concept of what is *normal* in terms of the form or functioning for a particular class of biological entities. While nature contains many prodigies, the normal can serve to orientate moral action (for example, in terms of whether that action tends to support what is regarded as normal functioning or produce divergence from it). What counts as normal is therefore a legitimate question but often one that is highly contested with regard to the extent to which norms are related to natural states or socially constructed, particularly in relation to issues of disability, medical intervention and enhancement.[99] Disability justice and rights scholars have made a range of moral arguments against selective technologies, from individual rights based arguments such as the right to life of people with disabilities, to arguments for the social and emotional value (e.g. vulnerability to contingency) of biological difference, to the value to humankind of conserving disability cultures, and the importance of the visibility of disability in establishing social attitudes, behaviour, and structures.

3.10 The valorisation of natural order that led to natural law philosophies of the medieval period finds an echo in the post-Enlightenment concept of moral duty and, in the contemporary world, in the flourishing of the human rights discourse that followed the Second World War.[100] This locates a ground for moral claims in the inherent and inalienable dignity that people have simply in virtue of being human, and to which each has an equal entitlement for the same reason. Respect for human dignity, and the rights that flow from it, governs and delimits proper behaviour towards others (and through respect for one's own dignity and the interests of others, may also have something to say about treatment of other animals and the natural environment).[101]

3.11 The effect of asserting human rights is essentially to mark out and defend limits of tolerable behaviour: the concept of inherent dignity proposes to supply an objective ground for making distinctions between acceptable and unacceptable uses of technology, between normal and abnormal conditions, therapy and enhancement and other morally significant categories. Those who derive moral judgments from rights considerations often make the further claim that, without these concepts, such distinctions are vulnerable to erosion, creating a 'slippery slope' into practices that offend moral intuition.[102]

Welfare and harm

3.12 Human rights are generally presented as grounds for claims against interference in the exercise of individual freedoms and, especially, against interference by public authorities. They ostensibly offer criteria to distinguish acceptable from unacceptable practices rather than offering a comparative evaluation of different possible courses of action. Such an evaluation may, however, be made on the basis of the consequences that different courses of action may be expected to produce. The theoretical position that the rightness or wrongness of an action is fixed by the consequences attributable to it is known as consequentialism. It offers the apparently simple rule that the action that should be selected is the one that produces the best consequences, all things considered. Utilitarianism is a variety of consequentialism that holds that consequences of action can be evaluated with reference to 'utility', which can be quantified, measured, aggregated, and subject to calculation to support a clear decision rule ('maximise utility') that will guide positive

[99] Canguilhem G (1991 [1966]) *The normal and the pathological* (New York: Zone Books). See also the response by the Center for Genetics and Society for arguments grounded in norms of medicine and reproduction. Assumptions made about quality of life of people affected by disabilities in debates about genome editing were highlighted in correspondence in *Nature* in 2015 (see: Shakespeare T (2015) Gene editing: heed disability views *Nature* **527**(7579): 446 and Wolbring G (2015) Gene editing: govern ability expectations *Nature* **527**(7579): 446.

[100] See: United Nations (1948) Universal declaration of human rights, available at: http://www.un.org/en/universal-declaration-human-rights/. See also: Glendon MA (2001) *A world made new: Eleanor Roosevelt and the Universal Declaration of Human Rights* (New York: Random House).

[101] We acknowledge the substantial literature on animal rights although it was not explicitly presented to us in evidence during our *Call for Evidence*.

[102] This position was put to us in evidence both from a Christian perspective and from a more secular position. For example, in the first fact finding meeting, by Robert Song, and also by respondents to the consultation, e.g. David A. Jones, from a Roman Catholic perspective, and Marcy Darnovsky, from a more secular position.

action.[103] Welfarism is a form of utilitarianism that identifies 'utility' with welfare.[104] This is useful for public policy because welfare is both broader than the private psychological states (such as pleasure and pain) and, though still personal to individuals, it is arguably subject to objective measurement.[105]

3.13 The strength of consequentialism in debates about biotechnologies and biomedicine is that it focusses attention on the expected benefits as reasons to support scientific freedom and excellence. It also requires us to consider what we might be giving up if we rule out certain technologies because we believe they are 'wrong' *in principle*.[106] On the other hand, this kind of approach generally depends on promises and expectations about what might be possible, or about what benefits or harms might result from using biotechnologies when they are deployed in complex and unpredictable real-life conditions. As such it is inherently speculative.

3.14 Since the consequences of biotechnology and biomedical interventions for welfare are not always or necessarily positive, the welfare balance sheet has to account for the likelihood and significance of both benefits and harms that might result. In some cases discussed in this report, the possible ramifications of a given application of biotechnology – the possible mechanisms of action and their endpoints – are too many and too convoluted to comprehend. The introduction of irreducible uncertainty therefore substantially undermines the apparent simplicity of the decision rule.[107] Where the consequences that can be envisaged include highly undesirable and irreversible, or catastrophic outcomes, precautionary modes of governance may be recommended. Whether or not a 'precautionary principle' should be invoked in relation to any of the applications of genome editing requires more specific attention in the contexts of proposed use.[108]

Social justice and just society

3.15 A particular concern that surfaced in our *Call for Evidence*, and that is found increasingly in relevant literature, is about the potential for the implementation of genome editing techniques in certain contexts (particularly biomedicine and human reproduction, but also agricultural and military applications) to have an impact on social, intergenerational or global justice (i.e. fair distribution of advantages or opportunities among different groups in a society, between one generation and the next or between nations, particularly the nations of the Global North and those of the Global South).[109] Such concerns require us to attend to the need to ensure that measures (such as the introduction of a new biotechnology) that affect welfare do so without discriminating unfairly among people.[110] Although people may be equal in dignity and the enjoyment of rights, they are not equally situated with regard to the benefits and harms of biomedicine and

[103] The canonical definition of utility, given by Mill, says only that "actions are right in proportion as they tend to promote happiness, wrong as they tend to produce the reverse of happiness." Mill JS (1971 [1863]) *Utilitarianism, Liberty and Representative Government* (London: Dent), at page 6.

[104] Sen A (1979) Utilitarianism and welfarism *Journal of Philosophy* **76**(9): 463-89.

[105] There are some conceptual difficulties, in that interpersonal comparison of welfare is difficult (perhaps even impossible). All consequentialisms have difficulties with counting (how do we count those who are affected within any given time period, how do we cope with consequences into the future – including for future generations – and are we allowed to discount, etc.

[106] The comparative approach dispenses with the need for a distinction between what is acceptable and what is not; it requires only that judgements relate to which of the available options produces more welfare than the others.

[107] On the distinction between risk and uncertainty, see *Emerging Biotechnologies* (Chapter 3 'The threefold challenge of emerging biotechnologies').

[108] The 'precautionary principle' and its cognates were invoked in a number of responses to our *Call for Evidence*. The use of the precautionary principle is highly contested and the principle itself is notoriously difficult to define, interpret and apply. This is discussed further in subsequent sections, in particular in relation to food (para.5.39) and the environment (para.6.30ff.)

[109] It is an acknowledged weakness of simple forms of consequentialism that they have little to say about how even or uneven the distribution of welfare should be among different people. (They may be interested in the experiences of people at all only insofar as they provide an index for the comparison between different possible states of affairs). Sen A (1979) Utilitarianism and welfarism *Journal of Philosophy* **76**(9): 463-89; see also response to *Call for Evidence* by the Center for Genetics and Society.

[110] A conception of justice as fairness was developed by John Rawls who, in *A theory of justice*, aimed "to generalize and carry to a higher order of abstraction the traditional theory of the social contract" as represented by Locke, Rousseau, and Kant." Rawls J (1971) *A theory of justice* (Cambridge, MA: Belknap Press), at page 3; 10.

biotechnology. Certain people may be disproportionately affected, may find themselves (perhaps involuntarily) in circumstances that render them particularly vulnerable, or be excluded from access to decision making or to benefits that are available to others. As a result, they may experience unfair discrimination and systematic disadvantage. It is argued by many that dignity and rights discourse is, in fact, insufficient to ground socially just action and that a specifically social justice perspective is called for: they consider it to be essential to put in place means for tracking social justice outcomes over time, and social justice goals in regulation of genome editing technologies.

3.16 The locus of responsibility for producing and addressing injustice, and the morally appropriate means of doing so, are often matters of dispute. One focus of such disputes is the extent to which differences are intrinsic or socially constructed (i.e. repose on shared assumptions about the world that are not inherent or necessary but are taken for objective fact, and often embedded in procedures, institutions or ways of thinking) and is the subject of a substantial literature.[111] Furthermore, while there is no question that women, people of colour, and disabled people (for instance) experience injustice, harm, and indignity in all societies, the forms that this takes can be highly culturally, socially and historically specific (thus US, Brazilian and English racisms have many differences, for instance).

3.17 In many cases, public policy measures are thought to be justified to forestall negative personal and social consequences, such as exacerbating existing inequalities and further disadvantaging people who contingently occupy positions of vulnerability. However, such measures may be controversial, particularly where they impinge on the interests of others. So, for example, the claim that the use of technologies that have the effect of reducing the incidence of disability (say, Down's syndrome screening or preimplantation genetic diagnosis) expresses and compounds negative attitudes towards people with disabilities has been asserted, by some, as a reason to prohibit their use; others would see such a measure as an inadequately justified intrusion into private life and liberty. There is an obvious public interest in such technologies in that the public pays for much of the basic research through public taxation.[112] But that is not all: in many cases the nature of the technologies involves citizens much more intimately, especially in conjunction with genomic science, bioinformatics and precision medicine, where they and their bodies supply the data and raw materials (for example, baseline and index data, biological samples) for scientific discoveries and technological developments.

3.18 As well as forestalling or redressing unjust treatment of individuals, public policy measures both reflect and affect the kind of society in which they are implemented, including the relationship between public and private, how and to what extent different groups and members participate in social life, how different priorities, preferences and values are resolved or tolerated, how equal or unequal in power, status and wealth its members are, and how open or closed the society may be. The features of any society are complex, interdependent and dynamic, but public policy measures often imply and express consistent common values and may be articulated around a collective vision of the desirable future state that they are expected to contribute to bringing about. These, in turn, influence the behaviours, institutions and culture of the society, for example whether it is welcoming or hostile to difference in terms of ethnicity, belief, appearance or ability. How genome technologies are taken up in a society can both betoken and consolidate essential features of a society by posing important questions about what is for individuals or for society to determine, how common challenges are met and how goods are distributed.

Governance and democracy

3.19 An anxiety running through many responses to our *Call for Evidence* was the need for clear limits to distinguish morally acceptable from unacceptable uses of genome editing. It is this concern

[111] Many everyday phenomena (e.g. money) depend, for their social function, on conventional assumptions (e.g. about their worth). Others (e.g. 'economic migrants') may be subject to distinctive consideration or treatment based on beliefs that are shaped by social forces and embedded in language. See, in general, Berger PL and Luckmann T (1991 [1966]) *The social construction of reality* (London: Penguin).

[112] Mazzucato M (2013) *The entrepreneurial state: debunking public vs. private sector myths* (London: Anthem Press).

that, in many cases, animates the appeal for some robust or even objective standard of judgement. The elaboration of such a standard in practice, however, often runs up against disagreement. Many, if not all, societies include people who cleave to different standards of value and take different approaches to moral questions. There is often no orthodox and generally accepted source of ready-made moral judgements on the complex implications of scientific research. Nevertheless, on matters of public policy (where there is a public interest at stake, as we discussed in the previous section) it is usually necessary to arrive at a single conclusion on any given question (even if different people may have different reasons for accepting it). Indeed, while there may be profound and earnest disputes about theories of value, as there are between scientists about quantum physics or evolutionary theory, the content of moral judgements may show a reasonable degree of co-incidence, as, for example, responses from different faith perspectives to our call for evidence showed.[113] The problem arises in finding a way to resolve areas of inconsistency where it is more important to do so than to tolerate exceptions (or where exception itself is intolerable).

3.20 Arriving at a conclusion on matters of public ethics is, in a general sense, a kind of political activity. Democratic governance purports to offer a procedurally legitimate solution to controversial questions in morally plural societies.[114] Yet, while they have the advantage of procedural legitimacy, all democratic procedures, to different extents, have a number of shortcomings: they are imperfect, slow, difficult and expensive (although for this reason they might answer the concerns of some moral conservatives that technology is moving ahead of society's ability to assimilate its implications to normative frameworks). Furthermore, although they are often bounded by the high level values of the society (e.g. conformity with established human rights), they effectively 'bracket out' second order ethical questions of substantive value and moral truth. Despite these shortcomings, democratic procedures nevertheless offer a plausible solution to, or way of coping with, the problem of the mutual adaptation of emerging biotechnologies and the normative frameworks within which they are deployed.[115] Much of the evidence we received pointed to the importance of having an open, effective and inclusive public sphere in which questions about genome editing could be raised and discussed, in which different positions and arguments could encounter each other, and the importance of democratic governance.

Conclusion

3.21 If, as we concluded in section 2, genome editing is a potentially transformative technology, one that both displaces current ways of doing things and subtly changes the nature of what is done, and, furthermore, redraws the horizon of expectations about what may and should be done, it may thereby produce tension with existing systems of norms. At the very least, the different speeds at which biotechnology and governance develop may put them out of kilter. Such tensions make visible and call into question the underlying values on which moral and legal norms repose. In the submissions received in response to our *Call for Evidence*, a variety of different approaches to dealing with this tension can be identified. These include conservatism that seeks to restrain the ebullience of biotechnology within existing moral frameworks, and ways to accommodate novelty while seeking to limit it within bounds that are grounded in norms derived from nature or established by convention. Other approaches would direct the development of biotechnology according to principles of welfare maximisation, and control it in accordance with principles of justice that both protect those in positions of vulnerability and are intended to realise a coherent vision of moral society. To the extent that there is a public interest in genome editing and to the extent that this interest makes genome editing the object of public policy (or of other social or institutional norms) a practical approach will need to be found that acknowledges that people both

[113] We received responses from the Church of England; the office of the Chief Rabbi; Hindu Council UK; the Sikh Missionary Society UK and the Muslim Council of Britain, as well as various Christian professional groups and NGOs.

[114] For an appraisal of democratic procedures in bioethics, see: Parker M (2007) Deliberative bioethics, in Ashcroft RE, Dawson A, Draper H, and McMillan JR (Editors) *Principles of health care ethics* (Chichester: John Wiley& Sons), pp.185-91.

[115] Presidential Commission for the Study of Bioethical Issues (2016) *Bioethics for every generation: deliberation and education in health, science, and technology*, available at: http://bioethics.gov/node/5678.

need a publicly coherent solution but may arrive at these questions with different thoughts about the nature of morality and different ways of valuing.

Section 4

Human health

Section 4 – Human health

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

[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

[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

[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.

Section 5

Food

Section 5 – Food

Outline

From the dawn of recorded history, and probably earlier, to the present day humans have sought to improve the quality and availability of food through selective breeding. New breeding techniques, including those involving genome editing, are described in the context of induced mutagenesis and other genetic engineering. The similarities and differences between genome editing and other alteration techniques are discussed. It is noted that the significance given to these similarities and differences may have significant implications for both the technology and food production. Different approaches to the regulation of foods and genetically modified organisms in the EU and North America are described and current areas of uncertainty noted. The potential impacts of uncertainty on science and industry are identified as matters of concern.

Reasons why genome editing may have less transformative potential in plant breeding than in animals are elaborated. Nevertheless, genome editing is a useful research tool for a variety of aims and has the potential to accelerate genetic gain in breeding programmes. The strong shaping of research by economic conditions that apply to commercial plant breeding are considered.

In animals, genome editing has made possible research that was not previously feasible. Limitations to achieving desired modifications are compounded by the low efficiency of the procedures used to produce genetically modified livestock, although genome editing has potential advantages over other approaches in terms of safety and controllability. Animal-based food products are subject to similar regulatory requirements as crop plants as well as additional requirements relating to animal welfare, which are outlined. The impact of genome editing on areas of livestock research relating to yield, animal health and environmental adaptation is described.

Many of the moral and societal issues are common to plants and animals, but they are not simply about securing adequate levels of consumption of safe, nutritious food. Lack of evidence of harm to human health of GMOs is cited as a reason to move to product regulation, based on substantial equivalence to existing products. This has not, however, removed concerns about uncertainties that science is unable to eliminate, the significance of which remains contested. Critical examination of the significance of uncertainty suggests it is grounded in a variety of different values, including attitudes towards genome technologies and consumer choice. The use and limitations of the precautionary principle and precautionary approaches are discussed. A critique of the framing of societal challenges is found to be indispensable in the formulation of ethical public policy responses. Different visions of future food production are considered in relation to their framing assumptions, revealing that what is needed for ethical public policy is an agreed presentation of the common challenge and the conditions for constructive engagement between different actors and interests.

Conclusions are drawn from the discussion about the significance of the emergence of genome editing as a driver for the critical reappraisal of moral and regulatory frameworks governing food production, the need to take a challenge-led approach to this reflection, and the need to consider the proper scope and jurisdiction of policy and regulatory measures

Introduction

5.1 Settled human societies have long sought to improve their food supply, in terms of quality (nutrition, preservation, appearance, taste etc.) and the ease of obtaining it (enclosed livestock, improved crops, etc.). This has exerted a tremendous evolutionary constraint that has left almost nothing that is commonly eaten today (except perhaps fish) biologically unaltered by human intervention and has rendered many wild antecedents extinct.[224] This section examines the potential impact of genome editing on plants and animals produced for food, principally for human consumption.[225] Uses of genome editing in wild animals and plants will be discussed in section 6. Genome editing of domestic plants and animals other than for food and related purposes, such as for show, competition or companionship will be noted where relevant.

[224] There is an irony, therefore in the fact that the first genetically modified animal approved for human consumption (by the US Food and Drug Administration) is the AquAdvantage salmon; see: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466214.htm.

[225] For the purposes of this part we discuss fungi along with plants since the issues are similar (noting that an FDA decision that a genome edited mushroom should not be regulated as a GMO has significant implications across both kingdoms – see: Waltz E (2016) Gene-edited CRISPR mushroom escapes US regulation *Nature* **532**(7599): 293.

Plants

5.2 The domestication of food crops began in the Neolithic period, over ten thousand years ago, a process that has continued to the present day. Domestication depends on mutagenesis: random or induced genomic mutations are fixed, giving rise to desirable traits, such as high yield, reducing genetic diversity in domestic populations and leading to a more homogeneous set of characteristics (phenotype).

Genome editing in the context of a range of plant breeding techniques

5.3 Many molecular techniques have recently been developed for use in plant (crop) breeding. These sit beside traditional breeding techniques that involve the selection of mutations that either occur naturally or are produced through the use of chemical mutagens or radiation. Selective breeding selects for overt (phenotypic) characteristics of an organism that are exhibited in a particular environment. In this case the genetic (or epigenetic) contribution to the phenotype, which may be related to a single gene variant or, perhaps, to hundreds of genes, may be unknown. Genetic engineering (including genome editing) generally involves the modification of specific genes to identify their effect on the phenotype and to reproduce this effect in populations. Whereas selective breeding can only work with variations that are present in the precursor organisms (as a result of natural or induced random mutagenesis) genetic engineering allows the introduction of characterised genes from other organisms, including from other species, to give rise to a phenotype that may be radically novel in the engineered strain.[226]

5.4 First generation plant genetic engineering most often involved the transfer of cloned genes from one organism to another (often using a bacterial vector, which inserts the gene at a random site in the organism) to produce a so-called 'transgenic' organism. Developments in understanding of the genome have given rise to a suite of New Breeding Techniques (NBTs), as they are collectively known. These have been enabled by advances in genome sequencing (including the increase in speed and reduced cost with next generation sequencing) and DNA assembly, both key underpinning technologies across molecular biology, as well as developments in data technologies and bioinformatics.

5.5 NBTs make directed changes to the genome without the need to introduce genes or regulatory sequences from another species.[227] The European Commission's New Techniques Working Group, established to review the applicability of Community GMO legislation, currently has under review the following NBTs:[228]

- Oligonucleotide Directed Mutagenesis (ODM)
- Zinc Finger Nuclease Technology (ZFN) comprising ZFN-1, ZFN-2 and ZFN-3
- Cisgenesis and Intragenesis
- Grafting
- Agro-infiltration
- RNA-dependent DNA methylation (RdDM)
- Reverse breeding
- Synthetic genomics

5.6 Whereas most of the products of first generation genetic engineering, known as genetically modified organisms (GMOs), involved the insertion of DNA, genome edited plants may be altered

[226] See also response to *Call for Evidence* by the Royal Society.
[227] An exception is the use of genome editing to insert transgenes using sequence-specific nuclease technology (SSN-3). See: Schaart JG, van de Wiel CCM, Lotz LAP, and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49
[228] See: http://ec.europa.eu/food/plant/gmo/legislation/plant_breeding/index_en.htm. For a comparative survey of some NBTs, see: Schaart JG, van de Wiel CCM, Lotz LAP, and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49.

in a way that is identical to natural or induced mutation, albeit that the mutation is specific and targeted. The ability to produce a specific and targeted mutation avoids the need to screen hundreds of thousands of crosses, (for example, between a crop and mutagenized plants or a wild relative containing the desired sequence) to identify those with the desired traits. The selective changes enabled by genome editing therefore significantly reduce the time and numbers of plants involved in achieving a desired mutation that might otherwise be sought by using methods of random mutation and selection.[229] Since genome editing techniques may also be used to introduce longer DNA sequences, including from other species, it is important to consider the nature of the product rather than the technology alone to determine safety and the regulatory process needed.[230] Similarities and differences between existing and prospective techniques of plant breeding are matters of current dispute, on which hang both moral and regulatory responses. The outcomes of these disputes may have far-reaching implications for how the technologies develop and, ultimately, how systems of food production evolve to meet global food security challenges.

Regulation of genetically altered food

5.7 The regulation of genetically altered food differs among jurisdictions in a number of respects, including the scope of regulation and how this is defined, the focus of regulation and the requirements placed on those subject to regulation. In the EU, a key distinction is made between genetically modified organisms (GMOs) and food that does not fall into this classification, albeit food that may have been subject to other alterations. All food and feed, including non-GMO food and feed, are subject to the 'General Food Law Regulation', which provides for the safety of food and animal feed, and to regulation by the European Food Safety Agency.[231] Additionally, a number of instruments apply specifically to GMOs in relation to containment and environmental risk (the release of GMOs into the environment, the movement of GMOs across borders, and the factors that can be taken into account), safety of GMOs for consumption by people and livestock, and traceability.[232]

5.8 From a food safety perspective, the key principles of all regulatory systems require demonstration that manipulation of the crop has not added a toxic or allergenic component and that, with the exception of the introduced genes, the composition of the GM plant is indistinguishable from the unmodified crop. In addition, from an ecological perspective, it is necessary to demonstrate that the GM crop will not become a weed, or threaten endangered or beneficial species. These principles clearly have value in relation to all new crop varieties, by whatever the means they are produced, although it is reasonable to debate the level of precaution and the extent of data required in different cases.

5.9 Other jurisdictions also have distinct provisions for the regulation of GMOs, although they may be engaged by different classification criteria. In the EU, the classification of GMOs is based on

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[229] Response to *Call for Evidence* by the British Society of Plant Breeders.

[230] "Some genome edited plants, those that contain no transgenes and only a minute change in the sequence of the DNA in a specific gene or genes, are different from GM plants. They are more similar to plants produced by mutagenesis technologies, which are not regulated as GM. Plants in which genome-editing technologies have been used to insert new DNA at a specific genetic location are similar to plants currently regulated as GM." Response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[231] Regulation (EC) No 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:en:PDF.

[232] See, respectively: Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, (available at: http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF0, amended by Directive (EU) 2015/412 as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory (available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L0412&from=EN) and Regulation (EC) No 1946/2003 on transboundary movements of genetically modified organisms (available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:287:0001:0010:EN:PDF); Regulation (EC) 1829/2003 on genetically modified food and feed (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R1829&from=en0); and Regulation (EC) 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0024:0028:EN:PDF.

whether the alteration has been made "in a way that does not occur naturally by mating and/or natural recombination", and is elaborated as 'at least' requiring the use of a listed technique.[233] This is conventionally thought to capture transgenic organisms but not those with alterations that might be achieved through natural breeding (however demanding), including those produced by cisgenics (where new genes are introduced from closely related organisms) and, arguably, certain genome editing protocols. In Canada, by contrast, all foods that are genetically altered, including by conventional breeding, are classed as 'novel foods' without further distinction. All novel foods require a pre-market notification to Health Canada (the Canadian federal department of health), following which a full safety assessment is made. This is done on the basis of the characteristics of the product itself, rather than the process by which it was produced.[234] In the US, genetically altered foods are regulated by the FDA. Where they are like substances currently found in food ('generally recognized as safe' – GRAS) they do not require separate pre-market approval. However, where a GMO product "differs significantly in structure, function, or composition from substances found currently in food," pre-market approval of the substance as a 'food additive' would be required.[235]

5.10 The subtlety and control possible with genome editing tools like CRISPR-Cas9, has led to strong proposals that products should not be subject to the extensive regulatory studies currently required for genetically-modified plants in Europe.[236] In many cases achieving the same DNA sequence and phenotype would be equally feasible through selective breeding. Genome editing also presents problems for analysis-based traceability, since the technique leaves no tell-tale genetic evidence in the final product.[237] However, it would be a commercial requirement for a new plant variety that it be registered for Plant Variety Protection, which guarantees intellectual property rights to breeders of new plant varieties.[238] This provides an additional reason to secure traceability, although this may depend on documented chains of custody rather than distinctive features of the product.[239]

5.11 The regulatory response to genome-edited foods in general remains uncertain. A number of crops produced using relevantly similar techniques have been approved for market in some countries.[240] Rulings have been handed down by the Animal and Plant Health Inspection Service (APHIS), an office of the US Department of Agriculture, that place genome-edited products in development

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[233] Directive 2001/18/EC, Art.2(2). The techniques are those listed in Annex I A, part 1; additionally, techniques listed in Annex I A, part 2 are deemed not to give rise to GMOs. Genome editing does not appear explicitly in either Annex.

[234] See: http://www.hc-sc.gc.ca/sr-sr/pubs/biotech/reg_gen_mod-eng.php.

[235] FDA (1992) *Statement of policy – foods derived from new plant varieties* (1992),available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm. See, generally, https://www.loc.gov/law/help/restrictions-on-gmos/usa.php#_ftn47.

[236] Jones HD (2015) Regulatory uncertainty over genome editing *Nature Plants* **1**: 14011; Strauss SH and Sax JK (2016) Ending event-based regulation of GMO crops *Nature Biotechnology* **34**(5): 474-7.

[237] […] the genes that code for the nucleases may be present at certain stages, but this is mostly temporarily, and they will not be present in the final product. Also, already technology is evolving to avoid the introduction of genes coding for the nucleases. The use of (pre- assembled) protein complexes may suffice in many instances in the future." Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie). In cases where the induced change is identical to those found in either natural or chemically-mutagenised populations, "it will be extremely difficult if not impossible to apply simple tests for contamination such as those currently used for screening product batches for contamination by transgenic seed. The burden of proof will therefore depend on the integrity of the ownership chain." Response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[238] Plant Variety Protection (PVP) protects the intellectual property rights of plant breeders by granting enforceable exclusivity for the marketing, sale and development of their registered varieties for a period of time (usually 20 or 25 years, or more for certain species such as trees). PVP is guaranteed by the International Convention for the Protection of New Varieties of Plants (UPOV Convention 1961, last revised 1991), which has 74 States Parties including most of the Americas and the global North, and by domestic legislation such as the US Plant Variety Protection Act of 1970 (PVPA), 7 U.S.C. §§ 2321-258. PVP overlaps but does not supplant other forms of intellectual property protection, such as patent protection.

[239] In a research interview, Professor Nicola Spence agreed that having no audit trail would make a product difficult to regulate, but she pointed out that there might be proxies for traceability: for example, isotope and mineral profiles can help to identify variety and potentially even what field it was grown in, demonstrating product integrity.

[240] For example, Cibus received market approval in the US and Canada for herbicide tolerant canola, obtained through the use of oligonucleotide-directed mutagenesis (ODM) and expect approval in other countries in 2018 (see: http://www.cibus.com/products.php).

beyond the special regulatory provisions that usually apply to GMOs.[241] The position of genome-edited products in the EU remains unclear at the time of writing and the European Commission has asked Member States not to take national decisions on the status of genome-edited products pending the release of an interpretative document.[242] This has led to concerns that persistent uncertainty is likely to lead to disinvestment, attrition of the research base (Europe accounted for 46% of research on plant NBTs in 2012) and failing international competitiveness.[243]

Applications of genome editing in food plants

5.12 The impact of genome editing techniques is, however, perhaps less revolutionary in plants than in relation to humans (see section 4) in the context of such a long history of changing the genetic characteristics of virtually all crop and ornamental plants. Plant breeding has been able to combine DNA sequences that occur naturally in a single plant, because discarding many thousands of crosses that do not have this combination is not considered to be an ethical issue, nor is the elimination of lines which contain an inherited 'abnormality'. In addition, mutation, either natural or induced, has been used to generate variations in DNA sequences, with those that produce useful phenotypic characteristics being retained. (In the gardening world, plants which contain natural mutations with a visible phenotype are called 'sports' and are highly sought after.) In some cases, it has been possible to cross different but related species to introduce traits, such as disease resistance, that do not occur within the species being improved. In plants, therefore, it has been possible to achieve many of the sorts of subtle changes in DNA sequence that are opened up in other organisms by genome editing techniques by cross breeding, or selecting natural or induced mutations that give rise to plants with the desired characteristics. The production of commercial GM crops, on the other hand, largely depends on the introduction of whole genes that do not occur naturally in plants (for example, the introduction of Bacillus thuringiensis genes from soil bacteria to give insect resistance and extensive changes to the EPSPS gene so that it codes for resistance to the herbicide glyphosate, which cannot be introduced by random mutation in natural populations).

5.13 In the laboratory, genome editing is proving to be a valuable research tool in plant breeding, including in gene discovery, producing knock-outs to study functional advantage and identification of 'safe harbours' (places where transgenes can be inserted safely without disrupting essential endogenous genes). It also supports current research into the integration of transgenes at specific positions, since the position of a gene in the genome affects its expression. Research uses have been proposed for genome editing that include traditional commercial targets such as improvements in yield and pesticide resistance. Other possible applications include inherent pest resistance (wheat resistant to powdery mildew,[244] bacterial blight-resistant rice,[245] and other causes of crop loss) that could reduce pesticide use, drought tolerance (e.g. for use in arid

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[241] Correspondence between the inventor (https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_inquiry.pdf) and the US Department of Agriculture Animal and Plant Health Inspection Service (https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf) regarding whether the 'non-browning' white button mushroom (*Agaricus bisporus*), edited to knock out some sequence using CC9, is genetically modified – although this is in relation to environmental impact rather than to consumption as food. A similar letter of comfort was received in response to a regulated article letter of inquiry from DuPont Pioneer regarding waxy corn variety produced using CRISPR-Cas9, which it intends to bring to market within a few years. (DuPont letter here: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_inquiry_cbidel.pdf; APHIS response here: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_response_signed.pdf). See also: http://uk.businessinsider.com/dupont-crispr-corn-in-stores-in-5-years). DuPont have made and agreement with Cariobou Biosciences – a spin-out from Jennifer Doudna's lab and one of the main IP claimants on the platform technology.

[242] See: European Parliamentary Research Service (2016), *New plant-breeding techniques. Applicability of GM rules*, available at: http://www.europarl.europa.eu/RegData/etudes/BRIE/2016/582018/EPRS_BRI(2016)582018_EN.pdf.

[243] "The knowledge generated through the research on NBTs, and the product innovations that are derived from their use, are already applied for commercial products in countries outside Europe. Prolonged absence of regulatory clarity for products derived from NBTs in the EU will hamper plant-related innovation in the EU and will mean a competitive disadvantage for EU-based plant breeders." Response to *Call for Evidence* by NBT Platform.

[244] Wang Y, Cheng X, Shan Q, *et al.* (2014) Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew *Nature Biotechnology* **32**(9): 947-51.

[245] Zhou J, Peng Z, Long J, *et al.* (2015) Gene targeting by the TAL effector PthXo2 reveals cryptic resistance gene for bacterial blight of rice *The Plant Journal* **82**(4): 632-43.

conditions, as a response to climate change and food shortages in developing countries),[246] and possible increases in nutritional benefit (e.g. nutritionally enhanced staple foods),[247] health benefit (e.g. decreased presence of allergens or anti-nutritional compounds)[248] and appearance (e.g. non-browning apples, which could reduce food waste).[249] Genome editing may also contribute to the development of plant-based industrial bioproducts, which could decrease dependence on oil-based products (see section 7 below).[250]

5.14 Where CRISPR-Cas9 shows most promise is in changing alleles in a targeted way – perhaps multiple alleles at a time – in basic breeding lines. Depending on the species, conventional plant breeding may require between seven and twenty-five years to generate desired characteristics and to introduce these into stable and uniform new plant varieties.[251] Genome editing offers the potential to reduce the shortest times for 'boutique' plants by two to three years and the longer timescales by more.[252] Knowledge of plant sequences linked to performance is now developing so quickly that it is possible to define an ideotype comprising so many desirable alleles that, statistically, it would be impossible to reach in a practicable number of generations of crossing. CRISPR-Cas9 could change the alleles in a targeted way in basic breeding lines, and thereby greatly accelerate genetic gain in the breeding programme by avoiding the need to go through economically unfeasible numbers of generations to achieve the desired combination of alleles by crossing.

5.15 There is also speculation that gene drives, which cause traits to be inherited preferentially, could be combined with editing systems and applied to plants. However, since crop plant breeding is controlled in any case, to secure the inheritance of desired traits, gene drives would be of use only in wild populations. A potential application, then, might be to control plant pathogens, or to control pests and weeds by conferring or reversing pesticide or herbicide resistance (see section 6, below).[253]

5.16 Genome editing faces many of the bottlenecks traditional to plant biotechnology: the time and effort required for delivery of DNA to plant cells (i.e. getting necessary reagents across the cell wall) and the regeneration of plants containing the programmed changes. Production of plants is labour-intensive, slow and requires significant investment in technical expertise and training, which is why private sector companies such as Dow AgroSciences, DuPont Pioneer and Cellectis have been major contributors to research and development.[254] Commercial firms are also free of certain demands that apply to academic research, such as the pressure for publication and to

[246] DuPont Pioneer is developing drought-resistant corn and more vigorous, hybridising wheat using CRISPR on a time line of 5-10 years; see reports at https://www.technologyreview.com/s/542311/dupont-predicts-crispr-plants-on-dinner-plates-in-five-years/.

[247] Haun W, Coffman A, Clasen BM, *et al.* (2014) Improved soybean oil quality by targeted mutagenesis of the fatty acid desaturase 2 gene family *Plant Biotechnology Journal* **12**(7): 934-40; Clasen BM, Stoddard TJ, Luo S, *et al.* (2016) Improving cold storage and processing traits in potato through targeted gene knockout *Plant Biotechnology Journal* **14**(1): 169-76.

[248] Schaart JG, van de Wiel CCM, Lotz LAP and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49.

[249] Nishitani C, Hirai N, Komori S et al. (2016) Efficient genome editing in apple using a CRISPR/Cas9 system *Scientific Reports* **6**: 31481.

[250] Response to *Call for Evidence* by the Agricultural Biotechnology Council.

[251] Response to *Call for Evidence* by NBT Platform.

[252] See responses to *Call for Evidence* by the British Society of Plant Breeders and GARNet. The likely time savings as a result of genome editing will depend on a number of factors but developments will still be subject to timescales of contingent processes, such as regulation and propagation of seed at sufficient scale for the commercial market, which take the bulk of the time.

[253] "In plants, gene drive could contribute potentially to sustainable agriculture by reversing pesticide and herbicide resistance [in weeds and pests]. More widely, it holds promise for the control of insect pests and vectors of disease." Response to *Call for Evidence* by BBSRC and MRC. The US source cited (The Wyss Institute for Biologically Inspired Engineering) notes that "By 2012, glyphosate-resistant weeds had infested 25 million hectares of US cropland." (see: http://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf).

[254] Evidence from fact-finding meeting on plant science and response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

demonstrate some types of impact.[255] However, the necessary protection of intellectual property through the lengthy research and development (R&D) process required to bring new products to market means that there is some uncertainty about how genome editing has been taken up. Agricultural biotechnology giants appear to be awaiting developments in genome editing by the academic research base and translational research by smaller biotech firms.

5.17 A question of significant interest is whether genome editing will help to deliver 'second and third generation' crops with improved characteristics such as enhanced growth, nitrogen fixing, stress tolerance and nutritional enhancements. Given the organisation of the innovation system and the concentration of resources in the hands of commercial firms, the products that are developed are likely to be those that have greatest commercial value, which to date have been principally herbicide tolerance and insect resistance, either because other beneficial changes have been of limited effectiveness, such as stress tolerance, or of limited commercial value, such as nutritional enhancement. Much may depend on decisions about regulation: the potential of genome editing techniques (in terms of decreased cost and technical difficulty, and increased speed) may revive the opportunities for small and medium-sized biotech companies in the agricultural area and unlock development of a wider variety of traits.[256] However, these may be easily depressed by regulatory burdens, such as those that apply in Europe in the case of GMOs in contrast to conventionally-bred lines.

Livestock

5.18 Unlike in plants, genome editing in animals has not merely accelerated research but made possible research that had been previously unfeasible.[257] Because the generation time in most commercial animals is long (typically many months) and their reproductive rates are often low (for example, one offspring per generation in cattle, although as many as 15 in pigs), the backcrossing strategies that allow native genes to be used so effectively in plant breeding are considerably less productive in the case of most livestock. On the other hand, the method of reproduction, which allows the possibility of embryological micromanipulation, makes animals more amenable to certain forms of editing.[258] There are said to be three principal challenges in genome editing with regard to livestock: the technology itself (and whether it can be scaled up to commercially worthwhile levels), securing regulatory approval, and farmer and public acceptance.[259] (The first two are discussed immediately below, the third under the heading 'Moral and societal questions identified', following an overview of the range of possible applications.)

Technical challenges

5.19 The majority of genetically engineered livestock are pigs produced by somatic cell nuclear transfer (SCNT), which yields piglets of predictable genotype.[260] Although SCNT has been the method of choice to produce cloned lines of gene targeted animals there are, nevertheless, limitations in terms of the relatively low viability of cloned embryos and the difficulty of achieving genetic manipulation of isolated nuclear donor cells.[261] Recently, the CRISPR-Cas9 system has become widely used, alongside ZFNs currently in use in pigs and other large animals, and TALENs in

[255] See also: Nuffield Council on Bioethics (2014) *The culture of scientific research*, available at: http://nuffieldbioethics.org/project/research-culture/.
[256] Evidence from fact-finding meeting on plant science.
[257] Tan W, Carlson DF, Walton MW, Fahrenkrug SC and Hackett PB (2012) Precision editing of large animal genomes *Advances in Genetics* **80**: 37-97; Rocha-Martins M, Cavalheiro GR, Matos-Rodrigues GE and Martins RAP (2015) From gene targeting to genome editing: transgenic animals applications and beyond *Anais da Academia Brasileira de Ciências* **87**: 1323-48; Wang Z (2015) Genome engineering in cattle: recent technological advancements *Chromosome Research* **23**(1): 17-29.
[258] 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.
[259] Research interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.
[260] 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.
[261] Ibid.

pigs, sheep and cattle.[262] As in other research, key challenges for large animal genome modification at present are to demonstrate that only defined changes are made at specific loci (avoidance of off-target effects) and to increase the efficiency with which changes can be introduced. Related to the issue of specificity, gene delivery to animals may be subject to 'insertional mutagenesis' in transgenic animals, which leads to unprogrammed gene suppression or expression.[263] Genome editing presents fewer sources of risk than conventional genetic engineering since it leaves no trace of the nuclease after it has performed its function and need not involve the introduction of extraneous (bacterial and viral) DNA as part of the delivery mechanism.[264]

Regulation of genetically altered animals

5.20 Insofar as animals and animal products might enter the human food chain (either directly or, for example, in the form of animal feed) they are subject, in most cases, to the same regulatory provisions as apply to plants. Thus, in the EU, they are similarly subject to the General Food Law and other Regulations and the Directive applying to GMOs (as applicable).[265] In the US, since the development in the 1980s of the 'coordinating framework', biotechnology products have been regulated based on their characteristics and intended uses rather than their method of production.[266]

5.21 However, to date, the only example of a GM animal being approved for direct human consumption is the AquAdvantage salmon, which was approved by the US FDA in late 2015, almost 20 years after the initial application, following an extensive review that looked at safety for humans, the impact of the change on the fish itself, and the environmental impact.[267] It is notable that, in the US, which, unlike the EU, does not require labelling of GM food, the FDA have stipulated that the AquAdvantage salmon should be labelled as genetically engineered, in recognition of the societal issues as well as scientific safety.

5.22 In addition to the health and safety provisions that apply to people working with animals in research and farming, and requirements about biosafety and environmental release that are similar to those applying to plants, research involving animals has additional levels of regulation relating to the welfare of the animals involved. In the UK this is overseen by the Animals in Science Committee (an NDPB that replaced the Home Office Animal Procedures Committee as principal source of advice to the Secretary of State, with whom the formal decision making power rests) under the Animals (Scientific Procedures) Act 1986.[268] Livestock breeding for food production is further regulated by a host of measures that include legislation and codes of practice designed to protect animal welfare on farms, in transport, at markets and at slaughter.[269]

Applications of genome editing in livestock

5.23 A number of applications of genome editing in animals have been reported or proposed. Traits currently under investigation mostly relate to improvements in yield, disease resistance, and adaptation to farming or environmental conditions. These traits have been pursued through other

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[262] Ibid.
[263] Tan W, Carlson DF, Walton MW, Fahrenkrug SC and Hackett PB (2012) Precision editing of large animal genomes *Advances in Genetics* **80**: 37-97.
[264] Ibid.
[265] Directive 2001/18/EC (environmental release), Regulation (EC) No 178/2002 (general food law regulation), Regulation (EC) 1829/2003 (genetically modified food and feed) and Regulation (EC) 1830/2003 (traceability and labelling).
[266] Carroll D and Charo R (2015) The societal opportunities and challenges of genome editing *Genome Biology* **16**: 242.
[267] The genetic alterations involve growth promoters that cause the all-female salmon grow to market size faster than farmed Atlantic salmon; see: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466214.htm.
[268] See: http://www.legislation.gov.uk/ukpga/1986/14/contents.
[269] See: https://www.gov.uk/guidance/animal-welfare.

approaches although here, as elsewhere, CRISPR-Cas9 genome editing may have advantages in terms of its relatively low cost, technical facility, speed and efficiency.

5.24 There are two basic approaches to augmenting yield: increased fecundity and more efficient conversion of inputs into outputs. Research and breeding programmes have focussed on a number of organisms where gains in reproductive efficiency can be made, for example, chickens that produce only female offspring for egg-laying, and cattle that produce only male offspring, which are more efficient than females at converting feed to muscle. [270] Applications to generate animals that are more productive with regard to inputs include, for example, pigs that can be fattened with less food, Brazilian beef cattle that grow large muscles, yielding more meat, and cashmere goats with greater muscle mass that also grow longer hair used in the production of soft sweaters.[271]

5.25 A number of genome editing applications relate to the health and welfare of animals. Many of these concern adaptation to environmental conditions, particularly those of intensive livestock farming, such as space and diet, and where close proximity to other livestock might facilitate the spread of infectious disease. These include hornless ('polled') cattle that can be kept in close proximity in confined spaces with lower risk of injury, and miniature pigs, which were originally purposed for their ease of husbandry in scientific research but which have since found a market as novelty pets.[272] Disease resistance is a particular area of active research given its commercial significance. One major advantage of engineered disease resistance in livestock is that it could, in principle, reduce the use of prophylactic antimicrobials in farming, as these have been cited as a significant cause of emerging antimicrobial resistance more generally.[273] Once again, commercial breeds are the main targets.

5.26 Resistance to viral pathogens is an area of major interest in poultry and pigs. For example, researchers at Roslin Institute in Edinburgh have produced a genome-edited Large White breed of pigs (in which the editing machinery was injected into the cytoplasm of the zygote), modified to be resistant to African swine fever virus.[274] This disease has a high (90%) mortality rate and represents a significant threat to the pig farming industry, currently menacing the borders of Europe. The pigs were edited to delete a few base pairs; this change results in an immune reaction emulating that of wild warthogs, which have a more effective immune response to the virus.[275] In the longer term it might be possible to contain swine and bird flu by genome editing their hosts, reducing their ability to act as reservoirs for zoonotic diseases that might affect humans and hence the frequent need for new human flu vaccines. To date, the technical strategies have achieved less success in chickens than in pigs.[276] Resistance to bovine tuberculosis could be useful in developing and developed economies, and more generally where animals resistant to certain kinds of disease and harsh environmental conditions would be valuable.[277]

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[270] New York Times (26 November 2015) *Open season is seen in gene editing of animals*, available at: http://www.nytimes.com/2015/11/27/us/2015-11-27-us-animal-gene-editing.html?hp&action=click&pgtype=Homepage&clickSource=story-heading&module=photo-spot-region&region=top-news&WT.nav=top-news&_r=1; Reardon S (2016) Welcome to the CRISPR zoo *Nature* **531**(7593): 160-3; response to *Call for Evidence* by Compassion in World Farming.

[271] Ibid.; Wang X, Yu H, Lei A, *et al*. (2015) Generation of gene-modified goats targeting MSTN and FGF5 via zygote injection of CRISPR/Cas9 system *Scientific Reports* **5**: 13878.

[272] Cyranoski D (2015) Gene-edited 'micropigs' to be sold as pets *Nature* **526**(7571): 18.

[273] O'Neill J, *et al*.(2015) Antimicrobials in agriculture and the environment: reducing unnecessary use and waste (HM Government and Wellcome Trust commissioned report of the Review on Antimicrobial Resistance), available at: http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf. The response to our *Call for Evidence* by Compassion in World Farming promotes a strategy for promoting 'positive health' in cattle through non-intensive farming methods. One element is to "Promote breeding for natural disease resistance and robustness and encourage a move away from genetic selection for high production levels as these appear to involve an increased risk of immunological problems and pathologies".

[274] Lillico SG, Proudfoot C, Carlson DF, *et al.* (2013) Live pigs produced from genome edited zygotes *Scientific Reports* **3**: 1-4.

[275] Ibid; The Guardian (23 June 2015) *Could these piglets become Britain's first commercially viable GM animals*, available at: https://www.theguardian.com/science/2015/jun/23/could-these-piglets-become-britains-first-commercially-viable-gm-animals.

[276] Reardon S (2016) Welcome to the CRISPR zoo *Nature* **531**(7593): 160-3.

[277] Research interview, Professor Hewinson, APHA.

5.27 Genome editing is of less interest in veterinary medicine than it is as a technique of cell-based therapy or gene therapy in humans; it is unlikely to be used for farmed livestock, although it may find a market among companion or show animals.

Moral and societal questions identified

5.28 Food production not only deals with one of the necessities of human life, but is also a matter of deep social significance, and one that is rooted in many characteristic cultural, ethnic, religious and social practices. Many of the questions relating to genomic manipulation of the foods that we eat are common to both plants and animals. They do not, however, simply invite empirical answers, however complicated but, rather, open up a complex of moral, political and scientific judgements. Those that surface as legal and regulatory questions, rest on conceptual distinctions (for example, between GMOs and non-GMOs), which, in turn, may be strongly imbued with moral and political judgements. They may involve attitudes to various factors such as how we value any potential harms and benefits to health associated with consuming animals, the environmental consequences of their diffusion, and the political and economic conditions of their production. From some perspectives 'genetic modification' seems less an empirical description than a moral designation, enshrined as a normative distinction. The use of genomic technologies and their consequences, however, must be seen in the context of possible alternatives: each has opportunity costs, with varying degrees of predictability, that involve people in collective acts of evaluation and moral reasoning, leading to societal choices that have further consequences for themselves and others.[278]

Confused terms

5.29 The sites and language of the discourse on genomic manipulation can be inaccessible to many interests and remote from consumers, both socially and geographically. Advanced biotechnology is predominantly a phenomenon of the rich world, although some of those most sensitive to its benefits and costs may be in the developing world. The technical language in which genomic manipulation is discussed by specialists in all disciplines (including both natural and social sciences) is frequently impenetrable to common understanding. This is a critical problem given the importance (acknowledged on all sides) of public engagement with biotechnology and food policy.[279] For example:

"Many people's concerns are, in fact, focused on the areas of scientific risk… However, as most people in the UK have not benefitted from a scientific education, they express concepts such [as] off-target and unexpected effects in less precise language. It is entirely unacceptable for any serious attempt to gauge public opinion and examine the ethical context of new scientific developments to dismiss the views of individuals who do not have the vocabulary to express themselves in scientifically-accurate terms."[280]

On the other hand, it is objected that:

> "One of the limitations faced by such a debate is that highly complex new science can rarely be explained in a soundbite, and this can be frustrating to the public and scientists alike, while providing an attractive area for campaign groups who can exploit public uncertainty."[281]

[278] Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.
[279] See, for example, Quinlan MM, Smith J, Layton R, *et al*. (2016) Experiences in engaging the public on biotechnology advances and regulation *Frontiers in Bioengineering and Biotechnology* **4**(3), doi: 10.3389/fbioe.2016.00003.
[280] Response to *Call for Evidence* by GM Freeze. From another perspective, Julian Hitchcock opines that "ethical debate is meaningless unless participants adopt a common language with shared, scientifically-informed, dispassionate meanings to key terms" (response to *Call for Evidence*).
[281] Response to *Call for Evidence* by the Agricultural Biotechnology Council.

5.30 To some extent different discourses make use of different lexicons: the public discourse may be filled with appeals to concepts of the natural and the artificial (and their analogues and cognates) which are found rarely, if at all, in the technical discourses (often because they are difficult to define in technical terms) although they are not without meaning.[282] Furthermore, terms that may seem superficially similar may have distinct meanings in different mouths.[283] The extent to which it is possible or necessary, for the effective governance of genome editing technologies, to present technical concepts in a way that non-specialists can understand and use, and whose responsibility it may be to make the concessions or efforts to achieve this understanding are moot points. However, meaningful political engagement depends upon finding a common language that is adequate to the presentation of a common problem rather than playing to a particular constituency.

Contested concepts

5.31 Perhaps the most contested concept in the vicinity of genome editing is that of the genetically modified organism (GMO).[284] The formal definition given in the relevant European Directive is conventionally glossed as the organism in question being produced using a particular kind of technique, especially one that inserts a transgene using recombinant DNA technology. The argument is put, particularly from the scientific research community, that genome-edited organisms should not be classified as GMOs where no transgene is involved, in which case the resulting organism is equivalent to one that could conceivably have arisen through conventional breeding techniques, without the inclusion of foreign DNA (from the use of a vector). In such cases, scientific analysis would, in principle, be unable to determine whether the characteristics of the organism had been produced by genome editing or by a 'traditional' breeding method.[285] In other words, the products of genome editing and 'traditional' breeding would in many cases be indistinguishable.

5.32 Others, nevertheless, assert that genome-edited organisms should be regulated as GMOs because the method of production is, in fact, one prescribed in the relevant Annex.[286] They base this claim on the alleged emphasis, in the European and (antecedent) Cartagena instruments, placed on "the use of in vitro techniques where the modification is induced by heritable material that has been prepared outside the organism" rather than the use of recombinant DNA technology specifically.[287] On this basis they argue that genome editing is significantly dissimilar to 'traditional' mutagenesis breeding so as to warrant more exacting regulation.

Inconsistent framings

5.33 What is at stake in the argument about whether food products developed using genome editing techniques are classified as GMOs is the kinds of enhanced regulatory scrutiny, political control, and marketing conditions (e.g. explicit labelling) that may be placed on particular instances of

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[282] See Nuffield Council on Bioethics (2015) *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/

[283] For example, the term 'traditional' (in the phrase 'traditional breeding techniques') can be a *faux ami*, being used within biotechnology discourse to designate breeding techniques that encompass the use of naturally-occurring or deliberately applied chemical mutagens and radiation in distinction from recombinant DNA technologies. "GE techniques are more precise than chemical or UV mutagenesis techniques, which have long been accepted as "traditional" approaches to breeding." (Response to *Call for Evidence* by BBSRC and MRC). This is at variance with the ordinary language meaning of 'tradition' as "A long-established custom or belief that has been passed on from one generation to another" (Oxford dictionaries).

[284] In their response to the *Call for Evidence*, the British Society of Plant Breeders expressed concern about the danger of genome editing being confused with transgenic (GMO) technology in public debate, which is largely 'political'. They paint an apocalyptic vision of our inability to meet global challenges of food security if genome editing technology were to be 'lost' as a result of this confusion (see below).

[285] This presents challenges for verifying traceability claims – see below.

[286] These others include Greenpeace – see response to *Call for Evidence*.

[287] Greenpeace "find that ODM [oligonucleotide directed mutagenesis] and SDN [site-directed nuclease] techniques fall into the category of direct modification using in vitro techniques, and hence would be classified as a GMO according to the EU and Cartagena definitions" (response to *Call for Evidence*).

food production.[288] This is non-trivial since, as discussed above, such measures may have a profoundly shaping effect on the agricultural biotechnology industry, the broader economy and the food supply.

5.34 At the heart of the regulatory system for food generally, and for GMOs especially – and this is common to almost all jurisdictions – is a concern, first and foremost, that the food should be safe for consumption. For prospective new products, this is established principally through an assessment of the risks it might pose to human health and wellbeing. Further considerations apply to risks to the health of animals and to the wider environment (for example, effects on biological diversity). In the case of novel products there is always some uncertainty and some room for dispute about what counts as relevant evidence. Accumulated evidence from the cultivation of genetically modified crops, however, has not demonstrated any exceptional risk to health.289 This has provided support to the increasingly frequent argument that GMOs should not be singled out for exceptional oversight but that all novel organisms should be assessed on the basis of their biological properties.[290] This means, essentially: on the basis of substantial equivalence to existing, well understood organisms.[291]

5.35 A reason for contemplating a move to product-based regulation is that there may be, in the future, products that are generated by the use of multiple techniques, which would present a challenge for classification on a process-based approach to regulation.[292]

> "The boundaries between established genetic modification (GM) and non-GM techniques will also become increasingly blurred as GE techniques develop. This raises questions about how organisms altered by any means should be regulated. Regulation based on the characteristics of novel organisms, however produced, would provide more effective, robust and future-proofed regulation than considerations based on the method used to generate them."[293]

5.36 A number of NGOs, nevertheless, continue to mount arguments for products developed by genome editing to be regulated as GMOs, and separately from other foods, on the basis of a putative risk to health or to the environment. This argument draws on claims about residual uncertainties: the uncertain effects on plant chemistry, biochemical pathways and unanticipated genomic interactions.[294] They suggest that biotechnology researchers are being misleading when they describe genome editing as 'precise' in order to emphasise its difference from first generation

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[288] Directive (EU) 2015/412 as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory was passed essentially to unlock the impasse to GM approval at community level by providing Members States with further opportunities to control production in their territories.

[289] The most recent analysis is the NAS/NAM report, *Genetically engineered crops: experiences and prospects* (2016), available at: http://www.nap.edu/catalog/23395/genetically-engineered-crops-experiences-and-prospects?version=meter+at+null&module=meter-Links&pgtype=article&contentId=&mediaId=&referrer=https%3A%2F%2Fwww.google.co.uk&priority=true&action=click&contentCollection=meter-links-click.

[290] See: European Academies Science Advisory Council (2013) *Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture*, available at: http://www.easac.eu/home/reports-and-statements/detail-view/article/planting-the.html. For the UK see: Biotechnology and Biological Sciences Research Council (2014) *New techniques for genetic crop improvement* , available at: http://www.bbsrc.ac.uk/web/FILES/Policies/genetic-crop-improvement-position-statement.pdf. For a further proposal, see: Huang, S, Weigel D, Beachy RN and Li J (2016) A proposed regulatory framework for genome-edited crops *Nature Genetics* **48**(2):109-11.

[291] "The question in this particular case is whether or not the familiarity that we have with the development of crops in which mutations and other small genetic alterations have been introduced in a blind manner, also applies for genome edited plants. Can we use that familiarity with the effects of classical mutagenesis? And does the way the conventional plant breeding sector develops, selects, evaluates, tests and registers new varieties also warrant enough safety for genome edited crops? Probably yes, because otherwise we would end up in situations where the same mutation has to go through a special legally binding registration process that requires a lot of testing when the mutation has been produced by genome editing, and none of this when the mutation has been achieved by conventional mutagenesis, or natural random mutagenesis (i.e. sunlight). This would be disproportionate and discriminatory." Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie.

[292] Research interview with senior Monsanto officer.

[293] Response to our *Call for Evidence* from BBSRC and MRC.

[294] See response to *Call for Evidence* by Greenpeace.

GM: they point to the mistake of equating 'precision' in the ability to manipulate nucleotide sequence with precision in the prediction or control of consequences or in terms of gene function.[295] Biotechnology researchers typically respond to these claims by alleging that NGOs are overstating the risks and exploiting uncertainties for political ends.[296] They argue that the designation of products developed using genome editing is unnecessary given the equivalence to 'traditionally developed' products.

5.37 Although these arguments are ostensibly about risk, what is perhaps most at stake is how and, indeed, whether the framing of risk captures what is important to different people about the production of food using NBTs, and whether these differences may be reconciled.[297] In the first place, a risk assessment only seeks to quantify perceived risk; it does not in any way show how that risk – or any residual uncertainties – should be valued.[298] It is very likely, in fact, that they will be valued by different people, with different interests and expertise, in different ways. It is a reasonable complaint that risks of harm and potential benefits of genetically altered products are not treated commensurately (although it is less a matter of managing the balance of risks and potential benefits of any one technology as finding the optimum mix of technologies and approaches to the perceived challenges).[299] Furthermore, risk assessment only applies to those things that have been identified as hazards. Again, views may differ about priorities: whereas most people might be expected to include safety of foods as a high priority, attitudes to environmental impact may differ and be confounded by cognitive dissonance and adaptive preference formation (as may be seen in responses to climate change).[300] As well as being difficult to predict, some factors, such as systemic environmental effects, are difficult to quantify, may only become manifest in the long term, and may be resistant to rational appraisal, despite being potentially of high importance.

5.38 These factors may explain why, to the consternation of many in the biotechnology field, public opinion research continues to reveal a sizeable minority who are concerned about the risks of genetic modification.[301] Although genome-edited plants might be de facto analytically indistinguishable from traditionally bred ones, the fact that a "technical procedure, which might be perceived as unnatural, is involved in producing these new plants" may be of concern to some people.[302] This is arguably a matter for the consumers rather than producers, since it allows consumers to exercise choices about the kinds of producers and production systems they wish to support through their purchasing. On the other hand, lack of product differentiation through labelling may contribute to economic lock-in (e.g. a world in which there is no ketchup without GM tomatoes due to non-GM ketchup being outcompeted). An important question is therefore who decides what information consumers should be able to receive. If it is right that consumers should be able to make such a choice on grounds that they themselves choose, labelling may be particularly important in the case of products developed by genome editing just because of the

[295] See response to *Call for Evidence* by GM Freeze.
[296] Cf. response to *Call for Evidence* by the Agricultural Biotechnology Council.
[297] See also: Douglas M and Wildavsky A (1982) *Risk and culture. An essay on the selection of technological and environmental dangers* (Berkeley: University of California Press).
[298] For the distinction between risk and uncertainty see Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/. For a different understanding of risk see Stirling A (2007) Risk, precaution and science: towards a more constructive policy debate *EMBO reports* **8**(4): 309-15.
[299] "Public debate most often focuses on potential benefit, while risk is narrowly defined around quantifiable hazards to either health or the environment." Response to *Call for Evidence* by GM Freeze.
[300] Runciman D (2015) A tide of horseshit *London Review of Books* **37**(18): 34-6.
[301] "The 2014 Public attitudes to science survey found that most people do not feel informed about genetically modified (GM) crops and a sizable minority (28%) say the risks outweigh the benefits for GM crops." Ipsos MORI (2014) *Public attitudes to science* (available at: https://www.ipsos-mori.com/researchpublications/researcharchive/3357/Public-Attitudes-to-Science-2014.aspx). For the US, see Funk C, Rainie L, Smith A, *et al*. (2015): *Public and scientists' views on science and society*, Pew Research Center, available at: http://www.pewinternet.org/2015/01/29/public-and-scientists-views-on-science-and-society/.
[302] In Europe, perhaps the majority (cf. Lucht J (2015) Public acceptance of plant biotechnology and GM crops *Viruses* **7**(8): 4254-81, at page 4270). According to Araki and Ishii (2015), "some people will demand to know which food products are produced from genome-editing plants, regardless of the degree of genetic modification." Araki M and Ishii T (2015) Towards social acceptance of plant breeding by genome editing *Trends in Plant Science* **20**(3): 145-9, at page 148.

absence of any distinguishing traces of the use of the technique in the resulting product.[303] Consequently, tracing through an auditable chain of custody becomes indispensable for that purpose.[304]

5.39 At the cornerstone of risk management in Europe is the much-discussed precautionary principle. This is notoriously difficult to define and to apply. Arguably, its 'elasticity' has been exploited to exert political control over the agriculture industry.[305] This is particularly apparent in relation to the exploitation of the margin of uncertainty, which science cannot eliminate, and in the discontinuity between the descriptive discourse of science, and the normative discourse of regulation. (It is possible to give a scientific description of the similarities and differences between genetic engineering and genome editing technologies but science cannot prescribe whether those technologies should be treated together or distinctly in respect of how their products are labelled and how they are traded in a competitive marketplace. What science can speak of more meaningfully is the relative scientific risk associated with different approaches, which is why, in our 2003 report, *The use of GM crops in developing countries*, we defined a 'precautionary approach' as a response to overly conservative application of the precautionary principle. The report drew attention to the fact that any choice, including one to maintain the status quo, had a benefit and cost profile that should be appraised comparatively.[306]) It is perhaps the narrow use of the precautionary principle as a crude 'decision rule' (given that the EU does not have the competence to make political decisions that impinge on member states' sovereignty) that forces sceptics to continue to mount arguments based on the apparently diminishing uncertainties about health risks and environmental contamination. This impoverished discourse around scientific risk assessment, however, obscures the more significant arguments about commercial freedom and equity, securing public benefits, the nature of the food security challenge and the desirability of different future states of affairs.[307]

Contending imaginaries

5.40 The situation to which agricultural biotechnology offers a set of possible solutions has been presented as a significant global challenge. "The Food and Agriculture organisation estimates that we need to increase food production by as much as 70% in the next 35 years but notes that agriculture already uses 40% of earth's landmass, 70% of fresh water and employs 30% of the human population. Agriculture and forestry are responsible for over 30% of our carbon emissions. The potential for improving plants using genome-editing technologies is considerable."[308] Likewise, political constraints on the use of new breeding techniques have been presented as a threat: some of our respondents noted that GM debate had 'killed the GM industry in Europe'.[309] The potential 'loss' of genome editing-based technologies, through being conflated with transgenic (GMO) technology in public debate, invites a vision of redoubled global challenge: "If

[303] In the research interview with a senior Monsanto officer a distinction was made between identification and traceability: genome edited products may be traced, but not identified.

[304] The relevant law in the EU is Regulation (EC) 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms.

[305] References to the precautionary principle occur prominently (in Art.7) of the General Food Law Regulation and its application to GMOs is the whole purpose of Directive 2001/18/EC, which covers deliberate environmental release and placing on to the market of GMO products.

[306] This point was reiterated and expanded in *Emerging Biotechnologies* (2012) [recommendation 1 on consideration of counterfactuals and opportunity costs.] See: Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[307] See Nuffield Council on Bioethics (2014) W*ritten evidence submitted to the House of Commons Science and Technology Committee inquiry: GM foods and application of the precautionary principle in Europe* (available at: http://nuffieldbioethics.org/wp-content/uploads/Submission_to_GM_inquiry_Nuffield_Council_on_Bioethics.pdf).

[308] Cited in response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.

[309] E.g. response to *Call for Evidence* by the British Society of Plant Breeders: "The GMO debate is clouded by political interests rather than remaining evidence-based, which has resulted in a *de facto* ban of GM in Europe and enhanced the global market power of breeding companies from outside the EU." They warn: "If it is decided that a European style GMO regulatory process must be applied to these products it will kill the potential for genome editing to be used to the benefit of European consumers."

genome editing is similarly lost, then all that remains to address the societal challenges of sustainable food production is classical breeding. This is unlikely to be sufficient to address the challenges of growing population, urbanisation and climate change."[310] However, an alternative framing suggests that this concern could betoken a premature or unwarranted hypothecation of societal and global challenges to particular technological solutions.[311] For example, responses to our Call For Evidence highlighted that intensification of food production was not the only available strategy to address global food security and that an equally substantial contribution could be made by tackling food waste or through revised farming practices and consumer preferences.[312] This draws attention to the need for an expanded framing that transforms more narrowly-defined 'problems' that invite technical solutions (in this case, problems of increasing food production and of reducing food waste) into potential components of a response to a broader societal challenge.

5.41 Expanding the parameters of the inquiry, however, also requires that attention be given to considerations that are both morally relevant and serve to lock-in particular technological pathways, such as the strong commercial and national economic interests involved.[313] The NBT platform has produced a fact sheet on the socio-economic impact of NBTs on the food supply chain in the EU that estimates that "a loss of 30% of the R&D in the EU would mean a loss in investment in high level equipment and jobs amounting to €210 million."[314] These interests sit starkly beside another important set of considerations that may be underrepresented in the discussion of global food security, namely the interests and agency of resource-poor communities, which are not natural markets for purely commercial products since the price of food there is necessarily low. Here, too, the impact of genome editing is potentially ambiguous and the response to it is a matter of political debate. "Just as government incentives are required for investment in neglected diseases that afflict developing countries, incentives may be needed to stimulate interest in the crops grown in these regions and in the growth of home-grown agri-tech ventures that can use genome editing technologies for the development of their own crops."[315]

5.42 Agricultural intensification appears to have significant momentum as a strategy for feeding the growing world population over the next 20 years or so, potentially bringing with it increasing susceptibility to infection and disease resistance.[316] Increasing dependency on biotechnology is itself a source of systemic vulnerability, with highly engineered products performing better in a controlled ecological niche but lacking robustness in response to environmental variation.[317]

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[310] Response to *Call for Evidence* by the BSPB. The response by the Agricultural Biotechnology Council cites Jack Bobo, former advisor at the U.S. Department of Agriculture, who has asserted that "the amount of food we need to produce in the next 40 years (is) equivalent to the same amount produced in the past 10,000 years." (Farmers Weekly (5 March 2013) *Food crisis will prompt GM foods rethink, says US aide*, available at: http://www.fwi.co.uk/arable/food-crisis-will-prompt-gm-foods-rethink-says-us-aide.htm. "What," they ask, "are the ethical considerations of not using gene editing technologies in plant science?"

[311] "The point of this scepticism is to draw attention to the error of committing prematurely to two sorts of potential frame: firstly, construing social 'challenges' as hypothecated to technological solutions (in general or particular) and therefore curtailing the exploration of other kinds of possible response; secondly, focusing the development of biotechnologies too tightly on solutions to particular challenges and therefore failing to be sensitive to the range of possible benefits they might bring, perhaps in radically different contexts." Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[312] High Level Panel of Experts on Food Security and Nutrition (HLPE) (2014) *Food losses and waste in the context of sustainable food systems. A report by the High Level Panel of Experts on Food Security and Nutrition* , available at: http://www.fao.org/3/a-i3901e.pdf. Cited by response to *Call for Evidence* by Compassion in World Farming.

[313] "The European plant breeding industry is a world leader in terms of innovation, representing a market value of more around EUR 8,6 billion. Additionally, of the more than 7000 companies in the EU seed sector, a significant portion (in some Member States up to 90%) are Small-to-Medium-Size Enterprises (SMEs), which are widely recognised as a major driver of innovation and economic growth. Many of these companies depend on innovation and access to technology to remain competitive." Response to *Call for Evidence* by the Agricultural Biotechnology Council) citing International Seed Federation (2013) *Estimated value of the domestic seed market in selected countries for the year 2012* and European Parliament, Directorate General for Internal Policies (2013) *The EU seed and plant reproductive material market in perspective: a focus on companies and market shares*, available at: http://www.europarl.europa.eu/RegData/etudes/note/join/2013/513994/IPOL-AGRI_NT(2013)513994_EN.pdf.

[314] See: http://www.nbtplatform.org/background-documents/factsheets/fact-sheet---socio-economic-impact-of-nbts.pdf.

[315] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.

[316] Research interview with Professor Hewinson (APHA).

[317] "Plants that are no longer capable of being an integral part of a biological system, that can no longer communicate and interact with beneficial soil organisms (eg mycorrhiza) except at a reduced level if at all, plants that require constant inputs to

Compassion in World Farming argue, for example, that genome editing might aggravate food insecurity if genome edited animals are used in industrial systems where animals are fed human-edible cereals and that contribute to environmental degradation.[318] What is presented as part of a solution may, they suggest, be a cause of the problem. Their vision, however, implicitly involves a move away from current levels of consumption of farmed meat and dairy products with perhaps unacceptable transition costs and deeply-rooted cultural resistance. The vision promoted by the UK's Royal Society, on the other hand, is one of 'sustainable intensification' that harnesses biotechnologies to address the multiple constraints of increasing population, water shortages, degradation of farmland and climate change.[319]

Box 5.1: Genome editing for PRRS

Porcine Respiratory and Reproductive Syndrome (PRRS) is a potentially devastating disease that threatens intensive pig production (the largest US facilities have barns housing up to 10,000 sows each). PPRS a causes significant reproductive loss in pigs and can move rapidly through a herd.[320] PRRS itself costs between 5% and 15% of production in any given year, since the disease is currently not well controlled and this means that affordability is impacted, both in terms of the product and the cost of corn previously fed to the infected animals.[321] The standard disease management protocol is the slaughter of exposed animals resulting in severe economic losses to the producer (or their insurer).

PRRS resistance is a recessive trait and not a readily observed phenotype (understandably so, given the standard disease management protocol). At least two major companies (Cibus and Genus) have research programmes using genome editing to engineer resistance to PRRS in order to improve the welfare of intensively farmed animals by reducing their risk of disease and reduce the economic risk to farmers. Genus quantitatively monitor more than 20 individual traits in pigs, all of which matter to their commercial performance, including feed conversion, efficiency, litter size, health and robustness (as a negative effect of genetic alteration represented by changes to these other traits might outweigh the benefits of PRRS resistance).[322]

The health of intensively farmed animals is a major area of concern. A pig may end up in receipt of, for example, 15 vaccinations in a very short life and the animal's immune system may not anyway be able to respond effectively. Intensive husbandry systems may contribute to pathogen emergence and evolution.[323] Research into the variable susceptibility of different breeds of pigs to viruses suggests that some level of resistance might be developed through breeding but it is likely in most cases that the pathogen would quite quickly adapt to the new strain.[324]

International projects in developing countries on intensification of pig production may compound both animal health problems and social inequalities. It is now better appreciated that subsistence farming plays a key role as part of an integrated farming system, also directly benefitting poorer farmers, and that there are also disease control benefits from this kind of farming. Other drivers for de-intensification relate to fostering development and sustainable global food production by focussing on improving the circumstances of poor farmers in the developing world.[325]

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the detriment of soil, pollinators, insects, biodiversity, healthy and ecologically sustainable agricultural systems – these are not the answer to current perceived and/or real problems. We need a different mindset that sees the interactions within ecosystems as the primary concern." Response to *Call for Evidence* by EcoNexus.

318 Response to *Call for Evidence* by Compassion in World Farming.

319 "As highlighted in the Royal Society report, *Reaping the benefits*, the pressures of soil degradation, water shortages and climate change are going to put pressure on crop plants and production will need to be sustainably intensified […]. Genetic techniques could also be used to introduce radical and highly significant improvements to crops for example: increasing photosynthetic efficiency, reducing the need for nitrogen or other fertilisers and changing annual plants to perennials." But: "Genetic technologies are not a 'silver bullet' and they will need to be combined with other expertise, for example agronomy to support crop production." Response to *Call for Evidence* by the Royal Society.

320 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.

321 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.

322 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus. See also: Whitworth KM, Rowland RRR, Ewen CL et al. (2016) Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus, *Nature Biotechnology* **34**(1): 20-22.

323 Research interview with Professor Drew (APHA) citing Drew, TW (2011) The emergence and evolution of swine viral diseases: to what extent have husbandry systems and global trade contributed to their distribution and diversity? *Revue scientifique et technique (International Office of Epizootics)* **30**(1): 95-106.

324 Research interview with Professor Drew, citing Ait-Ali T, Wilson AD, Westcott DG, *et al*. (2007) Innate immune responses to replication of porcine reproductive and respiratory syndrome virus in isolated swine alveolar macrophages *Viral Immunology* **20**(1): 105-18.

325 Research interview with Professors Drew and Hewinson (APHA).

5.43 One of the acknowledged challenges in identifying the appropriate frame for addressing societal challenges, such as food production, and expanding beyond a linear relation between a narrowly defined problem and a privileged solution, is to locate a suitable space of engagement in which different perspectives and knowledge may encounter each other. This requires allowing the political into the debate about biotechnologies, rather than seeking to resolve it on narrowly scientific grounds. "A recent John Innes Centre public dialogue project highlighted that the public was keen that scientists should consider the wider context of a problem, such as economic, societal and political factors which could be affecting food security, and take part in wider discussions on these lines."[326] This requires both openness and good will on all sides, and an orientation towards an agreed definition of the common challenge.[327]

Conclusion

5.44 Our objective in this interim report is to identify the distinctive moral questions, if any, raised by developments in genome editing, to consider the proper way of posing these questions (and, in doing so, to suggest how they might be addressed), and to prioritise these questions for the ethical deliberation that will follow in subsequent initiatives.

5.45 Many of the issues, such as animal welfare and the virtues or necessity of intensive agricultural systems, are not peculiar to genome editing, although developments in genome editing may bring additional factors into consideration or change the parameters of debate. Genome editing has quickly added another focus to these continuing debates. As a young technology, still undergoing continual technical refinement and exploring its potentialities, genome editing may appear to be drawn in as a vulnerable neophyte to abstruse and militant political debates. By changing the focus, however, genome editing may also insert a critical reflection into these debates, by challenging their parameters (introducing new future visions) and assumptions (such as the significance of the GMO/non-GMO disjunction), calling forth new evaluative frameworks and comparative analyses.

5.46 In relation to genome editing as a technique in food production, many of the questions have to do with classification boundaries – not so much where genome editing fits within existing boundaries but about the fitness of the boundaries, in relation to their underlying rationales, with consequences for regulation, labelling and public acceptance. Our general conclusion about framing ethical questions around genome editing seems appropriate in this instance too, namely, that the approach to normative questions – the approach that we should take in the second part of this project – should be to approach these questions from the point of view of the societal challenge on which genome editing has a potentially transformative impact, rather than the technological development itself. It is claimed that there is a need for harmonisation not only of regulatory controls but of ethical approaches.[328] By hypothesis, harmonisation of regulation may not be possible without harmonisation of ethical approaches. This leads to a second conclusion: that there is an outstanding question about the proper jurisdiction for both. The assumption that this jurisdiction, and its corresponding 'public', is that of the nation state or the regional bloc is therefore a question that requires further interrogation.

[326] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.
[327] The response from the Sainsbury Laboratory and John Innes Centre to our *Call for Evidence* contained a passage that could serve as a creed for engaged bioscientists: "It is important that scientists are seen as individuals not as a white-coated 'other'. We should represent ourselves as members of the community and our motivations and desire to achieve positive social outcomes should be communicated often and clearly. We should seek to describe the technologies that we employ in terms that are open and transparent, and should be clear about the relative similarity between plants with mutations induced by genome- editing technologies, those produced using older technologies and those that have acquired mutations without human intervention. Scientists should be sensitive to the role of food in human culture and religion and respect the beliefs of those that differ from our own while also speaking to the ethical need to produce sufficient nutritious food for our growing population." The same sentiment ought to apply, mutatis mutandis, to NGOs and to other actors within this public space.
[328] Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie.

Section 6

Environment

Section 6 – The natural environment

Outline

Human interventions increasingly have an impact on the biosphere. This chapter considers the potential ecological implications of deliberate or accidental releases of genome-edited organisms into the wild.

Three increasingly ambitious uses of genome technologies are discussed: genetically modified mosquitoes, bred to reduce the population of mosquitoes capable of acting as vectors of human disease, the elimination of non-indigenous predators to restore a national ecosystem and the revival and possible reintroduction of extinct species.

The concept of a 'gene drive' is introduced and its mechanism of action described in comparison to the propagation of genes through Mendelian inheritance and the fixation of variants in a sexually reproducing population by Darwinian evolution. Applications of gene drive technology are identified, including eradication of insect pests and disease vectors, reduction of invasive species and management of ecosystems.

The significant advantages of combining gene drive technology with the CRISPR-Cas9 genome editing system is described. Work to develop a low-cost, self-sustaining gene drive technology to control malaria-transmitting mosquito populations is described. Different possible refinements to the gene drive technique in order to improve the level of control, or to reduce or redress adverse outcomes are elaborated.

International, regional and some domestic legal and regulatory measures relating to the release into the wild of genetically altered organisms are noted. These include the Convention on Biological Diversity and its Cartagena and Nagoya protocols, and various regulatory measures in the EU, UK and US, as well as international guidance. Ambiguities and limitations of these instruments are suggested.

The nature of the moral and societal considerations relating to releases of genetically altered organisms into the wild is noted, and a number of considerations are discussed, including the importance of respect for the natural world and the sensitivity of natural ecologies, concern for the welfare of animals, risk of unpredictable ecosystem effects and ecological catastrophe. Responses to uncertainty, and the involvement of a broader engagement of a range of interests, actors and knowledge forms in precautionary approaches is considered. The prospects of reversing the effects of gene drives are examined and issues of technology transfer between rich and poor countries, and global justice are discussed. The need for responsible innovation approaches is highlighted.

Introduction

6.1 An important consideration for bioethics, at least since the appearance of genetic engineering, has been the environmental impact of human interventions. Human population requirements for food, energy and natural resources have changed the natural environment substantially, as have the outputs of industrial processes.[329] These effects have been so profound that many commentators and working scientists have adopted a way of referring to them as characterising a new aeon in geological time, the Anthropocene.[330] The environmental effects of human activity in general, including some of the consequences of biotechnology are, nevertheless, usually unintended or unavoidable by-products of the pursuit of a principal purpose such as agriculture and, as such, are usually counted on the 'risk' side of the balance sheet.

[329] References to the 'natural environment' are to the physical conditions that constitute the habitat for living things. The natural environment comprises distinguishable ecosystems regulated by processes that do not involve substantial human intervention, as well as relatively unbounded resources such as air and water. It is distinguished from conditions that have been fundamentally transformed by and are regulated by human activity (such as urban and agricultural areas). Ecosystems within the natural environment may be highly integrated (with high interdependency between elements) and dynamically stable over time. Because they are not in equilibrium, a disturbance (such as the introduction of a new microorganism, plant or animal species) may destabilise the ecosystem in a way that adversely affects the survival of certain organisms or produces conditions for other organisms to thrive, changing the composition of an ecosystem.

[330] This may be dated from the mid-20th century, from the industrial revolution in the late 18th century or even from the agricultural revolution in the Neolithic era depending on what evidence (for example, from the atmosphere or lithosphere) is adduced. The Stratigraphy Commission of the Geological Society of London has been considering a proposal to make the Anthropocene a formal division of geological time since 2009. The Guardian (29 August 2016) *The Anthropocene epoch: scientists declare dawn of human-influenced age*, available at: https://www.theguardian.com/environment/2016/aug/29/declare-anthropocene-epoch-experts-urge-geological-congress-human-impact-earth. See also http://anthropocene.info/.

6.2 We have previously (in sections 4 and 5) noted the risks of environmental contamination and the various biosafety measures that may be taken to avoid direct damage to the environment or to people as a result of uncontrolled exposure to, or release of, genome-edited organisms; we shall return to these in the section 7. In the present section we will consider the potential uses and environmental implications of genome editing, beyond 'contained' applications in research, medicine and industry, and managed cultivation and breeding in agriculture. The subject is therefore organisms that are intended for release into the wild (including those that are released deliberately to change the conditions of an existing ecosystem), their effects on animals, plants and microorganisms in the wild and the implications of these effects on human interests.

6.3 The uncontrolled impact of biotechnology on the environment may broadly abide by similar constraints and pressures that produce Darwinian evolution, speciation and extinction.[331] In section 5, we observed, in the context of agricultural biotechnology, how domesticated – especially highly engineered – organisms that appear to function well in the controlled, artificial environments for which they are bred (such as intensive agricultural systems with high fertiliser inputs, protected by herbicides and pesticides), are typically less well adapted than wild varieties to conditions outside these controlled environments (lacking immunological robustness, for example). Without the artificial inputs to which they are adapted, which form their particular environmental niche, domesticated organisms tend to fail to thrive and are out-competed by wild types. The concern has long existed, however, that a newly introduced organism, in certain conducive conditions, could take root and tip its surrounding ecosystem into a possibly unpredictable new state.[332]

6.4 Notwithstanding the large-scale risks of environmental impacts, if the use of biotechnology in general, and genome editing in particular, has the potential to produce large-scale systemic change it also raises the possibility of deliberately altering environmental conditions for a range of arguably beneficial purposes, including improved human and animal health, economic convenience, and even environmental geoengineering.[333] This may have the effect of making hitherto insuperable environmental constraints more tractable to human control, altering the range of achievable future states. In this section we look at the potential uses of genome editing of organisms for release into the wild, which may go on to grow and propagate naturally, before looking at a powerful use of genome editing in combination with 'gene drive' technology, which can cause the altered genotype to spread rapidly through a sexually reproducing wild population, by ensuring that it is inherited preferentially.

Use of genome technologies in the wild

6.5 Ecosystems are integrated open systems constantly subject to perturbation. Pests and diseases that may be remote or suppressed may spread and become epidemic, sometimes precipitously, as a result of the introduction of novel organisms or subtle changes in conditions.[334] One potential application of genome editing is effectively to arm a particular species in the continuous struggle between organisms. This might be accomplished by providing a selective advantage to that particular species, such as resistance to endemic disease.

[331] On extinction see Raup DM (1994) The role of extinction in evolution *Proceedings of the National Academy of Sciences* **91**(15): 6758-63.
[332] Doody JS, Soanes R, Castellano CM, *et al*. (2015) Invasive toads shift predator-prey densities in animal communities by removing top predators *Ecology* **96**(6): 2544-54.
[333] Royal Society (2009) *Geoengineering the climate: science, governance and uncertainty*, available at: https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2009/8693.pdf.
[334] Goldfarb B (2016) A virus is taming Australia's bunny menace, and giving endangered species new life *Science News*, doi: 10.1126/science.aaf4075 (published 17 February 2016).

6.6 Although mechanisms by which traits spread through a population may be understood at a theoretical level, their transmission is difficult to predict in complex, concrete circumstances.[335] While environmental release of organisms that are designated as 'genetically modified' is legally controlled (see below), the challenge of preventing such organisms from destabilising an ecosystem is probably usually not as great as the challenge of producing a modified phenotype capable of surviving as well as a wild variety and establishing itself in an uncontrolled environment.[336] Nevertheless, a number of high ambition initiatives using genome technologies have been proposed and developed with the aim of altering the characteristics of a breeding population of animals or altering the characteristics of the ecosystem of which they are a part.

6.7 An area in which research and innovation is advancing rapidly is the release of genetically modified insects. Oxitec Ltd, a company that started as a spin-out from academic research in the UK, has developed a genetically modified *Aedes aegypti* mosquito (the OX513A mosquito) using GM technology (i.e. not genome editing systems).[337] The *Aedes aegypti* is a vector of dengue fever in South America; Oxitec's focus is controlling the mosquito population, and therefore the likelihood of disease transmission, by breeding mosquitoes in which essential gene expression is inhibited, leading to cell death and the death of the insect before it reaches maturity.[338] Following trials in Grand Cayman, Brazil and Panama, the OX513A has received approval for use in Brazil where Oxitec has established a factory to scale up production.[339] The company has also applied the same technology to control agricultural pests, and has received approval for open field trials in Brazil and the USA for genetically modified Mediterranean fruit flies and Diamondback moths, which are the major pest affecting brassica crops.[340]

6.8 Another high ambition project potentially drawing on genome technologies was announced by the New Zealand government in July 2016. The aims of the project, under the rubric 'Predator Free New Zealand' are to eliminate ground-dwelling predators from the archipelago.[341] The public-private project will be started with NZ$28 million (£15.5 million) seed funding to explore a number of strategies targeted to the main non-indigenous predators (rats, weasels and possums). The strategies to be explored include the use of a 'Trojan Female Technique' (based on the

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[335] "While we can test for the safety and nutrient values of food plants, we do not possess the capacity for extensive testing of the behaviour of every genetic variant in a natural ecosystem", response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[336] This comment refers to the technical challenge only – it should not be taken to imply that it is unnecessary to be concerned about the possibility of catastrophic contamination.

[337] Oxitec Ltd. is a spin-out from Oxford University's Department of Zoology, acquired by Intrexon Corporation in 2015. It is pursuing similar aims to those of Target Malaria (see below) through a private enterprise business model. See: http://www.ox.ac.uk/news/2015-08-10-biotech-spin-out-be-sold-160-million-0.

[338] The effect can, in principle, be prevented by introducing an antibiotic – tetracycline – to the water in which the larvae feed allowing the larvae to survive and reproduce. Curtis Z, Matzen K, Neira Oviedo M, *et al*. (2015) Assessment of the impact of potential tetracycline exposure on the phenotype of *Aedes aegypti* OX513A: implications for field use *PLoS Neglected Tropical Diseases* **9**(8): e0003999.

[339] MIT Technology Review (17 February 2016) *Inside the mosquito factory that could stop dengue and Zika*, available at: https://www.technologyreview.com/s/600821/inside-the-mosquito-factory-that-could-stop-dengue-and-zika/. In April 2016 Anvisa, the Brazillian Health Regulatory Agency, granted Oxitec a special temporary registration authorising the research use of OX513A across Brazil. Under the conditions set by Anvisa, Oxitec and any public authority sponsoring the use of GM mosquitoes are still obliged to monitor all releases and to submit data to Anvisa on a regular basis. (See: http://portal.anvisa.gov.br/noticias/-/asset_publisher/FXrpx9qY7FbU/content/anvisa-decide-que-mosquito-transgenico-e-objeto-de-regulacao-sanitaria/219201/pop_up?_101_INSTANCE_FXrpx9qY7FbU_viewMode=print&_101_INSTANCE_FXrpx9qY7FbU_languageId=en_US).

[340] Waltz E (2015) Oxitec trials GM sterile moth to combat agricultural infestations *Nature Biotechnology* **33**(8): 792-3. APHIS, Environmental Assessment for the environmental release permit application for Oxitec diamondback moth strains, available at: http://www.aphis.usda.gov/brs/aphisdocs/13_297102r_fonsi.pdf; Approval document for the Mediterranean fruit fly in Brazil: http://www.jusbrasil.com.br/diarios/69287490/dou-secao-1-23-04-2014-pg-51. See also: http://www.oxitec.com/agriculture/our-products/medfly/ and http://www.oxitec.com/agriculture/our-products/diamond-back-moth/.

[341] See http://predatorfreenz.org/; BBC news (25 July 2016) *New Zealand aims to become predator-free by 2050*, available at: http://www.bbc.co.uk/news/blogs-news-from-elsewhere-36883799.

introduction of females carrying mutated mitochondrial DNA that leads to the production of male offspring with impaired sperm function).[342]

6.9 A more speculative use of genome technologies is to reconstruct and reintroduce extinct species from the genome upwards. Revive and Restore, a company funded with Silicon Valley venture capital, promises 'genetic rescue for endangered and extinct species', and has a 20-year roadmap to bring back extinct species like the passenger pigeon and the heath hen, as well as more exotic ambitions like the woolly mammoth.[343] This latter may be a fanciful, if headline-grabbing suggestion: it would be necessary to rebuild genomes from archaic samples discovered in permafrost; furthermore, almost nothing is known about mammoth reproduction, and there is little expertise in artificial fertilisation of elephant eggs (which may be required) and *in vitro* culture of elephant embryos. A more technically plausible possibility, however, although one that is far more ethically complex, is the revival of archaic humans such as *Homo neanderthalensis*, using synthetic biology and existing cell reconstruction and culture techniques.[344]

Gene drive

6.10 Existing wild varieties tend to be best adapted to their environment and, all other things being equal, the spread of a trait through a naturally reproducing population is favoured only when the trait has a selective advantage (which human intervention provides, in effect, for agriculturally valuable organisms).[345] Researchers have discovered a way to accelerate the population-wide propagation of a trait by using a technique called a 'gene drive'.[346]

6.11 In most cases the prevalence of a gene variant in a population can be adequately explained by natural selection, whereby a relatively successful variant provides the organism with a competitive advantage so that organisms carrying that variant reproduce more (and *vice versa* for relatively unsuccessful variants). Thus, a beneficial variant can be expected to increase in prevalence in a population despite the fact that it is inherited through exactly the same mechanism of genetic recombination as a less beneficial (or even a harmful) variant. There are cases, however, in which the higher prevalence is explained not by the relatively high survival rate of the organisms carrying the gene variant but by preferential inheritance of specific variants through 'intragenomic conflict'.[347] Gene drive systems promote the spread of genetic elements through populations by ensuring they are inherited more frequently than by Mendelian inheritance would predict. This

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[342] Gemmell NJ, Jalilzadeh A, Didham RK, Soboleva T and Tompkins DM (2013) The Trojan female technique: a novel, effective and humane approach for pest population control *Proceedings of the Royal Society B: Biological Sciences* **280**(1773): 20132549.

[343] See http://reviverestore.org/. Cf. Shapiro B (2015) Mammoth 2.0: will genome engineering resurrect extinct species? *Genome Biology* **16**(1): 228.

[344] In 2013 it was misreported that Harvard geneticist George Church was seeking a human surrogate mother to assist with experiments to produce a Neanderthal baby. Although the story turned out to be false, the proposal is more technically feasible than the revival of many other species that have been suggested. See: http://www.bostonherald.com/news_opinion/local_coverage/2013/01/harvard_professor_blasts_neanderthal_clone_baby_rumor_web.

[345] A textbook example is the adaptation of the British peppered moth, from pale to dark, as a result of the blackening of its habitat by coal pollution in the early nineteenth century. The underlying genetic mutation has recently been identified as a transposable element (see box 6.1): Van't Hof AE, Campagne P, Rigden DJ, *et al*. (2016) The industrial melanism mutation in British peppered moths is a transposable element *Nature* **534**(7605):102-5.

[346] For a thoroughgoing examination of the uses of gene drive and questions arising, see National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and. The overarching conclusion of this report is that "There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials."

[347] Intragenomic conflict occurs when particular allele or gene variant within a genome is preferentially inherited at the expense of other variants, with selection occurring through a mechanism operating at the level of the cellular reproduction rather than at the level of the organism. Spencer HG (2003) Intragenomic conflict *Encyclopedia of Life Sciences*, doi: 10.1038/npg.els.0001714. See also: Burt A and Trivers R (2008) *Genes in conflict: the biology of selfish genetic elements* (Cambridge, MA: Harvard University Press).

allows a genetic variant to spread through a population even though it does not provide a selective advantage to the organism. In particular, so-called autocatalytic homing endonucleases are commonly referred to as 'gene drives'[348]

6.12 The concept of a 'gene drive' was coined by Christopher Curtis at the London School of Hygiene and Tropical Medicine in 1968, who proposed using translocations (rearrangements of genetic material) to drive anti-pathogenic genes into wild vector species.[349] It remained theoretical, however, until Austin Burt and colleagues at Imperial College, London, demonstrated that such a nuclease-based gene drive functions in an animal (the mosquito *Anopheles gambiae*) in 2011.[350] Gene drives aim at population, species or ecosystem-level genetic engineering. There are natural and synthetic gene drive systems.[351] Synthetic drives are being explored to understand how populations might be altered through adding, disrupting, or editing genes, or by propagating traits that influence fitness or reproductive capacity.

Box 6.1: Gene drive systems

Natural gene drives were recognised in the middle of the last century in various species.[352] For example, in *Drosophila* (a small fly) the *segregation distorter* (*sd*) locus ensures that one of two alleles is preferentially transmitted to offspring, a phenomenon known as meiotic drive, whereas typical parental alleles have a 50% chance of being inherited. Segregation distorters occur in other species, such as *sk* in the mould *Neurospora* spp and the mouse *t*-haplotype. Transposable elements (TEs), sometimes referred to as 'jumping genes' may also be thought of as natural gene drives: they are DNA segments able to move from one location to another (transposition), sometimes with replication, and independently of selection. Transposable elements are widespread throughout nature (they are present in bacteria, plants and animals) and are exemplified by a class of transposable elements in *Drosophila* called P elements, which originated in the mid-twentieth century and have since spread through all *Drosophila* populations.[353]

In general, transposition is catalysed by a transposase enzyme encoded by the transposable element; transposase has some functional parallels with homing endonucleases, which also catalyse natural gene drives. Homing endonucleases are enzymes that recognise and cut rare (in the range of tens of base pairs) DNA sequences. Because the recognition cut site in a naïve DNA sequence matches sequences on either side of the homing endonuclease gene (HEG), repair of the cut results in a copy of the homing endonuclease gene being copied into the cut site – a process termed 'homing'. This means that in diploid cells (cells that have two copies of each chromosome), where one copy of a chromosome contains a homing endonuclease gene and one does not, the naïve chromosome may acquire a copy independently of selection. These classes of genes or genetic elements may all be considered natural gene drives because they facilitate their own perpetuation with little dependence on conferring a selective advantage

Applications of gene drive technology

6.13 Gene drives have thus far found no application in the production of domesticated plant varieties as breeding is highly controlled anyway. They might, however, be useful in controlling plant pathogens, or to control pests and weeds by reversing pesticide or herbicide resistance.[354] They also have promise as methods for control or eradication of insect pests and vectors of disease directly, including diseases affecting livestock and humans.[355] These include many insect-borne tropical diseases, such as dengue, malaria and Zika. Applications that have been suggested include the reduction or elimination of invasive (or otherwise undesired) species such as cane

[348] Gantz VM and Bier E (2015) The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations *Science* **348**(6233): 442-4.
[349] Curtis CF (1968) Possible use of translocations to fix desirable genes in insect pest populations *Nature* **218**(5139): 368-9.
[350] Burt A (2003) Site-specific selfish genes as tools for the control and genetic engineering of natural populations *Proceedings of the Royal Society of London Series B: Biological Sciences* **270**(1518): 921-8; Windbichler N, Menichelli M, Papathanos PA, *et al*. (2011) A synthetic homing endonuclease-based gene drive system in the human malaria mosquito *Nature* **473**(7346): 212-5.
[351] Sinkins SP and Gould F (2006) Gene drive systems for insect disease vectors *Nature Reviews Genetics* **7**(6): 427-35.
[352] Response to *Call for Evidence* by Target Malaria.
[353] Spradling AC, Bellen HJ and Hoskins RA (2011) Drosophila P elements preferentially transpose to replication origins *Proceedings of the National Academy of Sciences* **108**(38): 15948-53.
[354] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre; BBSRC and MRC.
[355] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

toads, lionfish, giant African snail, kudzu, black rat and zebra mussels.[356] This might in principle be achieved using gene drive by altering sex ratio, reducing fertility, or producing chemical sensitivity.[357] In the future, gene drive systems could be introduced into vectors of livestock and plant disease, so that they are no longer able to transmit specific pathogens.[358] In addition, it may be possible for gene drive systems to be used to accelerate the propagation of traits within mammalian genomes, for example to disseminate disease resistance within a breed of pigs.[359] Ultimately, gene drive systems could expedite the expression of human preferences over the composition of the biosphere.

6.14 Among the most promising and well advanced applications of gene drive systems are those targeting wild insect populations that transmit tropical diseases that affect human populations. It has been proposed that synthetic gene drives could be released to control mosquito populations or their ability to transmit malaria, dengue fever, yellow fever and Zika.[360] Strategies for the use of gene drive systems include making the insect vectors that would otherwise carry them refractory to disease-causing parasites and altering the sex ratio in favour of males (because only female mosquitoes bite).[361] For example, the Target Malaria research consortium aims, by using a gene drive system, to inactivate specific genes in two species of *Anopheles* malaria-transmitting mosquitoes, *Anopheles gambiae* and *Anopheles arabiensis*.[362] (Worldwide there are approximately 3,500 mosquito species, although only about 40 *Anopheles* species are able to transmit malaria in a way that presents a substantial risk to human health.)

Converging technologies: CRISPR-enabled gene drive

6.15 The convergence of gene drive systems with the CRISPR-Cas9 genome editing system to effect specifically targeted genomic modifications has been described as a 'game changer' in the field.[363] Gene drive systems that harness CRISPR-Cas9 have been applied in research on different organisms including mosquitoes and yeast.[364] In April 2015, a US group reported a very efficient gene drive system for *Drosophila* which is capable of driving a mutation into 97% of offspring in just two generations.[365] In this system, the gRNA, the edited (desired) version of the target gene

[356] Webber BL, Raghu S and Edwards OR (2015) Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *Proceedings of the National Academy of Sciences* **112**(34): 10565-7; Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[357] Webber BL, Raghu S and Edwards OR (2015) Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *Proceedings of the National Academy of Sciences* **112**(34): 10565-7.

[358] Alphey L and Alphey N (2014) Five things to know about genetically modified (GM) insects for vector control *PLoS Pathogens* **10**: e1003909, available at: http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003909.

[359] Professor Bruce Whitelaw, personal communication, September 2016.

[360] See Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401; Carvalho DO, McKemey AR, Garziera L, *et al*. (2015) Suppression of a field population of Aedes aegypti in Brazil by sustained release of transgenic male mosquitoes *PLoS Neglected Tropical Diseases* **9**(7): e0003864, available at: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003864; Alphey L and Alphey N (2014) Five things to know about genetically modified (GM) insects for vector control *PLoS Pathogens* **10**: e1003909, available at: http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003909; National Academies of Sciences, Engineering, and Medicine (2016) Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

[361] See for example: Galizi R, Doyle LA, Menichelli M, *et al*. (2014) A synthetic sex ratio distortion system for the control of the human malaria mosquito *Nature Communications* **5**: 3977.

[362] Target Malaria grew out of a university-based research programme and remains a non-profit initiative, funded by a core grant from the Foundation for the National Institutes of Health (FNIH) through a programme of the Bill & Melinda Gates Foundation. Participating laboratories receive additional funding from a variety of additional sources. See: http://targetmalaria.org/who-we-are/.

[363] Ledford H (2015) CRISPR, the disruptor *Nature* **522**(7554): 20-4.

[364] Gantz VM, Jasinskiene N, Tatarenkova O, *et al*. (2015) Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi *Proceedings of the National Academy of Sciences*, doi: 10.1073/pnas.1521077112 (published online 23 November 2015); DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5.

[365] Gantz VM and Bier E (2015) The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations *Science* **348**(6233): 442-4.

and Cas9 endonuclease are combined into a cassette (denoted 'GDC' in the diagram in box 6.2), so that Cas9 and the gene modification are inserted together into the target gene. Such a cassette has the potential to create a self-sustaining gene drive, a process that has been described as a 'mutagenic chain reaction'.[366]

Box 6.2: CRISPR-enabled gene drive

BoxText style An experimental use of a CRISPR-Cas9 enabled gene drive in *Drosophila* involved a gene modification that had been introduced on one chromosome copying itself onto the unmodified sister chromosome.[367] This mechanism ensured that during the process by which the gametes (sperm or egg) are produced, every gamete genome harboured a copy of the gene drive. This meant that when the flies bred with wild animals lacking the gene drive element, they passed it on to the resultant 1-cell embryo. In the 1-cell embryo, the gene drive mechanism rapidly recapitulates; the gene drive copies itself onto the naïve chromosome inherited from the wild animal so that now both corresponding chromosomes contain the drive. Normal DNA replication and cell division subsequently ensures that all cells of the embryo and ultimately the adult contain the gene drive.

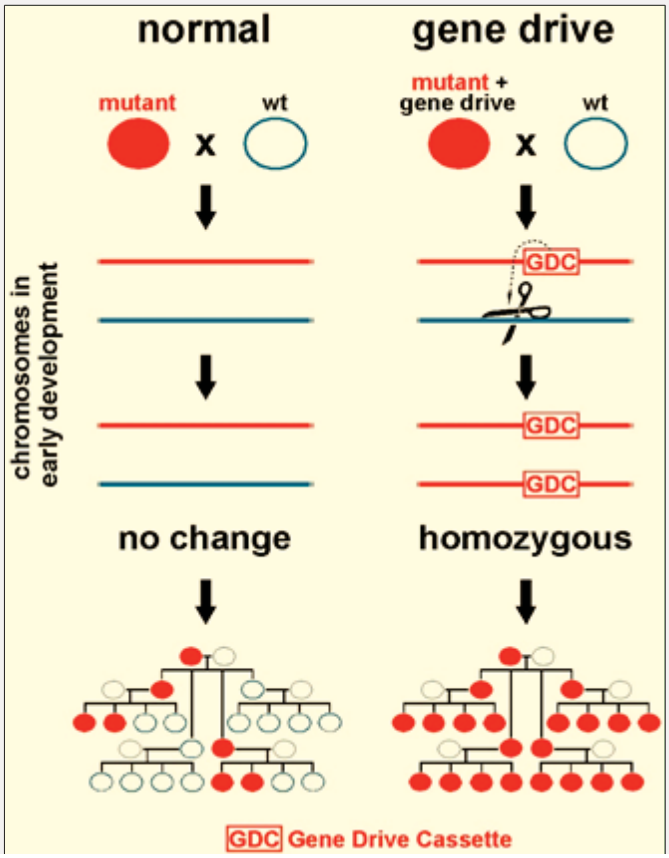

Illustration provided by Dr Tony Perry, member of the Working Group.

6.16 Strategies currently under investigation involve protein engineering endonucleases to act in a similar way to homing endonucleases discussed above These would disrupt essential genes such as genes involved in reproduction (so as to reduce fertility or unbalance the sex ratio in favour of males) or genes that are required for pathogen transmission.[368] The CRISPR-Cas9 system offers transformative potential in this context because until its arrival there had been no effective system for specific gene knockout in mosquitoes.[369] The Target Malaria research is currently targeted to sub-Saharan Africa where around 90% of all malaria-related deaths occur (currently Burkina Faso,

[366] Ibid.
[367] Ibid.
[368] Response to *Call for Evidence* by Target Malaria; see also http://targetmalaria.org/.
[369] Evidence from fact-finding meeting on animal research.

Mali and Uganda). Adoption of the CRISPR-Cas9 system has made gene drive potentially more accessible and relatively easier to apply than previous methods, which would provide a low-cost, self-sustaining technology, that could transform the mosquito population over epidemiologically relevant time and region. This is critical in a context where resources to fight the disease are severely limited, making it unfeasible to rear sufficient numbers of modified mosquitoes that would be required for an inundative approach.[370] It has a potential added advantage of reducing dependence on environmentally harmful insecticides and freeing low resource health care systems from having to provide anti-malarials or buy immunisations. Target Malaria envisage deployment within five to 10 years (from 2016) to allow safety and efficacy testing and risk assessment but – assuming all goes well in the interim – it is likely to be longer that this before they can begin to make a difference in practice.

Refinements for control of gene drives

6.17 Gene drives have a number of limitations. Because they depend on the natural cycle of sexual reproduction in the target organism, the pace of diffusion is limited. They are therefore most effective in fast-reproducing species, such as insects, and in simple genetic systems. Furthermore, gene drives cannot escape evolution, so the gene drive components or other features of the host organisms may mutate and these mutations enter into evolutionary selection. Non-homologous end joining tends not to preserve sequences at the break termini; and gene drive function would need to be controlled because of DNA damage and immune processes that are only partly understood.[371] Modelling the effects of gene drive systems in the wild is a complex problem and appropriate risk assessment and modelling tools will need to be developed for each set of circumstances. These will need to establish to what extent gene drives are likely to be prescriptive in the wild. To the extent that a given drive cannot be prescriptive (and yet the perceived benefits outweigh the attendant risks) mitigation strategies will have to take into account the ecological impact of the drive, which might make it impossible to restore the initial conditions of the system. The relative power of gene drive and natural selection is a subject of current investigation and discussion including a recent substantial report by the US National Academies of Science, Engineering, and Medicine.[372]

6.18 A number of refinements have been proposed and developed to gene drive technologies strategies to address the potential risks of uncontrolled proliferation of self-sustaining gene drives in wild populations.[373] '**Reversal drives**' could be deployed to overwrite changes introduced by an initial drive.[374] '**Immunizing drives**' could be introduced to block the spread of unwanted gene drives by pre-emptively or reactively altering target sequences so that they would not be recognised by the first drive. '**Precision drives**' could be more finely constrained to particular species or subpopulations by targeting sequences unique to those groups so as to reduce the possibility of transmission between (closely-related) species. Using two drives, the first to alter a defined population to provide a unique target and the second to make the desired phenotypic alteration could help to ensure that the second drive does not leave a controlled population, such as an island habitat.

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[370] See paragraph 6.7 above.

[371] Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[372] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and See also: DeFrancesco L (2015) Gene drive overdrive *Nature Biotechnology* **33**(10): 1019-21; Unckless RL, Clark AG and Messer PW (2016) Evolution of resistance against CRISPR/Cas9 gene drive *bioRxiv*, doi: 10.1101/058438 (posted online 11 June 2016).

[373] Some of these risks and benefits, and a typology of refinements to enhance safety, are outlined by Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[374] This would leave only the guide RNAs and the gene encoding Cas9 as evidence of past editing; see Esvelt et al. 2014 (op. cit.). It could not, however, reverse any ecological effects of the initial drives that had taken place in the interim.

6.19 Other strategies might limit the population suppression effects of releasing a gene drive system, avoiding species extinction and ecological risk. '**Sensitizing drives**' might make a target organism sensitive to environmental chemicals. These could work in different ways, for example, by reversing known mutations that confer resistance to pesticides or herbicides, by introducing an enzyme that would metabolise an environmentally neutral compound into toxin within the organism, or by swapping a conserved gene for a version that is strongly inhibited by a particular small molecule. 'Evolutionarily unstable drives' could also be used, whereby reproductive genes carried by a standard drive on an autosome (i.e. not on a sex chromosome) would suppress the target population but natural selection would select against this loss of function within the population. Maintaining the effect of the initial drive would therefore require periodic release of the modified type.[375]

6.20 Population suppression could also be controlled by releasing '**interacting drives**', which would only cause the effect when the two drives encounter each other through mating. Finer control could be achieved by further releases of one or other of the drives to suppress one or other of the two genotypes or induced new species.[376] '**Split gene drives**', in which biallelic mutations introduced with an sgRNA-only transgene cassette can spread only when combined with an unlinked Cas9-only transgene cassette, are currently considered to have the greatest potential safety. This allows homozygous individuals lacking the Cas9 transgene to be isolated easily in subsequent generations.[377] The split system has been developed in brewer's yeast (*Saccharomyces cerevisiae*), in which it was shown to be as efficient as a gene drive construct encoding both Cas9 and sgRNA together.[378]

Law and regulation

6.21 Given the potential ecological consequences of the environmental release of genetically altered organisms a multi-layered regulatory system exists to govern this area of application. The International Convention on Biological Diversity (CBD) entered into force on 29 December 1993.[379] It has three main objectives: (1) The conservation of biological diversity, (2) The sustainable use of the components of biological diversity, and (3) The fair and equitable sharing of the benefits arising out of the utilization of genetic resource. Article 8(g) calls on Contracting Parties to "Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health".[380] Art.19(2) calls on Contracting Parties to "take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties […] on mutually agreed terms."

6.22 The *Cartagena Protocol on Biosafety* is an international agreement that aims to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking also into account risks

[375] Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.
[376] Ibid.
[377] DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5.
[378] DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5; Akbari OS, Bellen HJ, Bier E, *et al*. (2015) Safeguarding gene drive experiments in the laboratory *Science* **349**(6251): 927-9.
[379] See: https://www.cbd.int/convention/text/.
[380] Synthetic biology is not explicitly addressed in the CBD or its protocols. However, Decision XII/24, of the Conference of Parties to the CBD encourages the use of precautionary approach in respect of organisms, components and products resulting from synthetic biology. It also establishes an Ad Hoc Technical Expert Group to, inter alia, review the sufficiency of existing provisions, including consideration of the applicability of the Cartagena Protocol, examining the similarities and differences between living modified organisms (as defined in the Protocol) and organisms, components and products of synthetic biology techniques, and to develop an operational definition of synthetic biology. (See: https://bch.cbd.int/synbio)

to human health.[381] It gives effect to the 'precautionary approach' set out in Principle 15 of the *Rio Declaration on Environment and Development*.[382] Parties to the Protocol must ensure, among other things, that release of any living modified organism is undertaken in a manner that prevents or reduces the risks to biological diversity, also taking into account risks to human health. It was adopted by the Conference of the Parties to the Convention on 29 January 2000 and entered into force on 11 September 2003.[383]

6.23 The *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization* is an agreement that aims at sharing the benefits arising from the utilisation of genetic resources in a fair and equitable way.[384] It entered into force on 12 October 2014. It is based on the principle (Article 5) that equitable returns should be made for the provision of genetic resources by donor countries (i.e. non-exploitation of one party by another, rather than global solidarity). Article 8(b) calls on Parties to "Pay due regard to cases of present or imminent emergencies that threaten or damage human, animal or plant health, as determined nationally or internationally. Parties may take into consideration the need for expeditious access to genetic resources and expeditious fair and equitable sharing of benefits arising out of the use of such genetic resources, including access to affordable treatments by those in need, especially in developing countries." Article 23 has text relevant to technology transfer between countries but in relation to the achievement of the objective of the protocol (set out in Article 1) – which is about equitable benefit sharing contributing to the conservation of biological diversity and the sustainable use of its components (*i.e.* not about global health and technology transfer).[385] The CBD and protocols are implemented via European Union Law (including a directly applicable Regulation on in the Nagoya Protocol) and transposed through various pieces of domestic legislation in the UK under the responsibility of the Department of the Environment, Food and Rural Affairs (Defra) and its agencies (and corresponding bodies in the home countries).[386]

6.24 Regional and national legislation exists in different areas relating to the environmental release of modified organisms. For example, in the EU, this is governed by Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms (GMOs). This contains a definition of GMOs that applies also to plants, although the applicability of this definition to organisms altered using genome editing techniques is currently (in August 2016) contested.[387] In the US (which is not a signatory to the *Cartagena Protocol*) biotechnology products that have potential environmental impacts are covered by the National Environmental Policy Act of 1969 and presumed to be subject to the 1986 Coordinated Framework for the Regulation of Biotechnology, under the combined aegis of the Food and Drug Administration, US Department of Agriculture and Environmental Protection Agency. The Centers for Disease Control and Prevention also has regulatory competence where the product involves a threat to public health.[388] The Co-ordinated Framework is currently under review and there is potential inconsistency with regard to which agency has the responsibility and capacity to regulate gene drive, genome-edited and genetically modified animals.[389] This was highlighted by the fact that Oxitec's genetic

[381] See: https://bch.cbd.int/protocol.
[382] "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." See: http://www.unep.org/Documents.Multilingual/Default.asp?documentid=78&articleid=1163.
[383] See: https://bch.cbd.int/protocol/parties.
[384] See: https://www.cbd.int/abs/.
[385] The UK has signed, ratified and become party to the CBD, the Cartagena protocol, and the Nagoya protocol. The US has signed but not ratified the Convention, and is not a party to it.
[386] Regulation (EU) No 511/2014 on compliance measures for users from the Nagoya Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization in the EU (available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0511).
[387] See section 5, paragraph 5.31ff. above.
[388] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.
[389] Ibid.

modification technology fell to be regulated by the FDA (in the case of the GM mosquito) and the USDA (in the case of the GM diamondback moth) depending on the application.[390]

6.25 The anticipated sites of release for many genome-edited organisms are, however, not in Europe or the US but in tropical areas of sub-Saharan Africa, southern Asia and South America. Indeed, given the potential diffusion of organisms across national borders in the wild, national laws and policies are often insufficient on their own, although they can provide an important a focus for debate and engagement. There is, furthermore, a concern that conventional provisions on biosafety such as those in the *Cartagena Protocol* and regional and local instruments that transpose its basic provisions, do not take adequate account of the distinctive potential for environmental impact of gene drive systems arising from preferential inheritance. This has led to a recognised need for more specific guidance in relation, for example, to GM insects. In response to this, the World Health Organisation (WHO) has agreed guidelines on the release of GM mosquitoes (June 2014) which propose standards of efficacy and safety testing comparable to those used for trials of other new public health tools, with the aim of fostering quality and consistency among processes for testing and regulating new genetic technologies.[391] The guidelines assemble the known standards and guidance based on current research evidence and extensive professional and public consultation.[392]

Moral and societal questions identified

6.26 There are potentially significant benefits for human beings to be achieved through the use of genome editing to modify the natural environment, and scientific development in this area is, *per se*, undoubtedly consonant with identifiable moral purpose (the Baconian ideal of the 'relief of man's estate' as we noted in section 3). The moral reason to pursue and implement these developments may, however, be tempered by other considerations. These include whether there are limits to this aim itself or to how it may be pursued, whether achieving relief of one kind entails a countervailing burden that makes it morally unjustifiable (and whether this anthropocentric aim should be given paramountcy over others that may be morally valuable, such as the welfare of animals or preservation of habitats), as well as and whether relief for some entails injustice to others. Concerns about environmental risk from human interventions in open ecological systems, where the implications of biotechnology use are not only its immediate effects but also causes of a multitude of further potential adaptations in turn, invite a different kind of moral reflection to what usually surrounds relatively 'closed' interventions in biomedicine and, to an extent, in domesticated plant and livestock farming. Rather than being concentrated on the rightness of particular decisions, these concerns have spatial and temporal extension, often with uncertain limits; they invoke a different range of values and principles, such as those of sustainability, stewardship, precaution, and global and intergenerational justice.

Valorisation of the natural

6.27 Opposition to species control and (especially) engineered extinction may follow from placing significant value on outcomes other than human wellbeing.[393] One position holds that that it is simply wrong to interfere in life processes in this way, whatever the aims or the certainty of

[390] Information supplied by Sarah Hartley, University of Nottingham. See also: National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

[391] World Health Organization (2014) Guidance framework for testing of genetically modified mosquitoes, available at: http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/.

[392] This was commissioned by TDR (the Special Programme for Research and Training in Tropical Diseases) and the Foundation for the National Institutes of Health. TDR is a global programme of scientific collaboration that helps facilitate, support and influence efforts to combat diseases of poverty. It is hosted at the WHO, and is sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and WHO. FNIH is a US charitable body established to manage funding and research in support of the mission of the NIH in the US and across the world.

[393] See section 3, above.

achieving them.[394] Another position holds that respect for the natural world and its non-human inhabitants should limit the activities of human beings. This may be of concern for the suffering of individual animals that it is thought to entail (which might suggest that it is likely to vary according to the type of animal involved).[395] Even where it does not necessarily entail animal suffering, however, this worry may still arise from concerns about the maintenance of ecological integrity and stability.[396] This raises questions about the valorisation of the 'natural' and the 'natural' relation of beings.[397] Occurrences of the normative use of 'natural' and its cognates (as opposed to its use as a descriptive adjective contrasting with 'deliberate' or 'artificial') were, however, rare in the evidence we gathered and almost always appeared in the critical literature as a 'straw man' to attack rather than as a value earnestly advanced. It may well be, therefore, that these positions are either largely absent from the discussion of genome editing (or not yet engaged with it), or have become sublimated in more sophisticated presentations.[398] In any case, it is not apparent that this is an important token in current debate, and the risk of participants 'talking past' each other in debate has not (yet) materialised.[399] The state of public discourse may be an issue that merits further attention as this debate develops in the public sphere.

6.28 Caution with regard to environmental release of genome-edited organisms is more likely to arise from concerns about different kinds of threat than from attributions of intrinsic value. Such concerns have two dimensions: moral confusion and natural catastrophe. The first concerns threats to the order and classification of beings on which knowing how to respond to them depends.[400] This appears to be less of a real concern in the case of the organisms considered for environmental release than for boundary questions about reproduction and food discussed in sections 4 and 5. The concern about ecological catastrophe resulting from interference with the 'balance of nature', however, is particularly common in relation to release of modified organisms. This holds that natural processes have operated to produce metastable ecosystems, which human intervention risks perturbing with unpredictable and potentially catastrophic results (although these results may be catastrophic only from an anthropocentric point of view).[401]

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394 Nuffield Council (2015), *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/.

395 Research interview with Professors Glyn Hewinson and Trevor Drew (APHA).

396 Background extinction rates not due to human action are almost imponderable, however calculations have been made that suggest that 0.1 extinctions per million species-years is "an order-of-magnitude estimate of the background rate of extinction." See: Pimm SL, Jenkins CN, Abell R, *et al*. (2014) The biodiversity of species and their rates of extinction, distribution, and protection *Science* **344**(6187), doi: 10.1126/science.1246752, at page 2). The figure the authors give for present extinction rates are approximately 1000 times higher although causes are impossible to attribute reliably. The figures might support a suggestion that even if human activity is not exceptional in kind, its effects are, directly or indirectly, exceptional in magnitude.

397 For a discussion of the term "natural" see evidence supporting the Nuffield Council's 2015 work on *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/. The paper explores five accounts of 'naturalness' deriving from: (1) scepticism about the link between nature and value, (2) belief in the 'wisdom of nature', (3) belief in natural purpose, (4) reactions of disgust and monstrosity to the 'unnatural' and artificial interventions, and (5) God and religion.

398 See *Ideas about naturalness in public and political debates about science, technology and medicine*, op.cit.

399 This risk was identified in *Ideas about naturalness in public and political debates about science, technology and medicine.* It may, however, be because the debate is at an early stage and has not yet fully penetrated the media, Parliamentary debate, the reports of civil society organisations, and advertising and labelling, where our earlier research found it to be used in a value-laden way. But in any case, such usages are generally performative: if participants in a public debate are 'talking past' their apparent interlocutors, it is usually because they are talking past them to their sympathisers, refusing the terms of engagement, with consequences for the quality of public debate.

400 "Our responses to disorder and anomaly are strongly socially structured […] they are elicited by threats to our dominant systems of classification and the generally accepted ways of applying them. Structured in this way they are protective of the existing institutional order." Barnes and Dupré (2008) *Genomes and what to make of them* (Chicago: University of Chicago Press), at page 212. Christian theology has consistently offered a principle of order guaranteed by God (cf. the medieval trope of the Great chain of being (*scala naturae*).

401 The best known expression of the idea that the earth and its component sub-systems function globally as a self-regulating system that can be perturbed in unpredictable ways by interventions that appear to be safe or low risk in the short-term is found in the Gaia hypothesis, put forward by James Lovelock in Lovelock J (1979) *Gaia: a new look at life on earth* (Oxford: Oxford University Press).

6.29 There are biosafety concerns about genome editing research and gene drive research involving genome-edited organisms, where the system is not deemed ready for environmental release.[402] (A fuller discussion of biosafety follows in section 7.) These, however, elide substantially with questions about the consequences of environmental release, which in turn bear on decisions about if and when release may be appropriate.

Precaution

6.30 As noted above, the *Cartagena Protocol* gives effect to the 'precautionary approach' set out in Principle 15 of the *Rio Declaration on Environment and Development*.[403] Whereas the latter is ostensibly about intervening to prevent uncertain environmental degradation the former explicitly orientates this towards the introduction of possible new environmental threats from biotechnologies. Precautionary approaches are proposed where substantial uncertainties cannot be excluded which, due to system effects, might include serious and undesirable consequences that may not be apparent in the short term, and which, were they to materialise, would be difficult or impossible to reverse.[404] In view of the gravity of potential consequences, precautionary thinking requires that reasonable measures should be taken to anticipate them before there is scientific proof of their likelihood.[405]

6.31 Precautionary approaches have been discussed at length in the relevant literatures and in a number of Nuffield Council publications.[406] This is not the place to engage in a sustained discussion of the coherence, persuasiveness or utility of the various formulations. Two points from previous discussions bear emphasising, nevertheless, relating to symmetry and to scope. The first is that a precautionary approach should be distinguished from simple risk assessment in that it requires account to be taken not only of the foreseeable consequences of a proposed intervention but also of the consequences of *not* making the intervention, and of the possible alternatives to the proposed intervention.[407] Rather than simply assessing 'risks', this focuses attention on the complex profiles of possible benefits as well possible harms of a range of alternative options, as well as the distribution of those consequences among different people and places.[408] The distinction between technology-focussed and challenge-focussed perspectives on precautionary thinking becomes evident in the contrast between proposals to trial GM mosquito technology in order to gather evidence on which to base a risk assessment and those to engage

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[402] On biosafety with regard to gene drives see: Akbari OS, Bellen HJ, Bier E, *et al.* (2015) Safeguarding gene drive experiments in the laboratory *Science* **349**(6251): 927-9.

[403] The related 'precautionary principle' is also a vexed feature of the regulation of environmental release of GMOs in the European Union.

[404] On the use of a precautionary approach in the expectation of hidden tail risks see response to *Call for Evidence* by Rupert Read; Taleb NN, Read R, Douady R, Norman J, and Bar-Yam Y (2014) *The precautionary principle (with application to the genetic modification of organisms)*, working paper of the New York University Extreme Risk initiative, available at: http://arxiv.org/pdf/1410.5787v1.pdf.

[405] Formulations of this principle vary considerably but most encapsulate the basic idea of acting to mitigate a credible threat to human wellbeing or the environment in the absence of evidence or consensus of the likelihood of it occurring. This is often said to shift the burden of proof onto innovators to demonstrate that their innovation is not harmful. The strict principle has been criticised as being incoherent (see, for example, Sunstein CR (2005) *Laws of fear: beyond the precautionary principle* (Cambridge: Cambridge University Press). It has also been suggested that it should be regarded more as a rhetorical and political gambit than as a decision tool.

[406] See: Nuffield Council on Bioethics (1999) *Genetically modified crops: the ethical and social issues* and *The use of GM crops in developing countries: a follow-up discussion paper* (2003), available at: http://nuffieldbioethics.org/project/gm-crops/; Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice, and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/; Nuffield Council on Bioethics (2014) *Submission to the House of Commons Science and Technology Committee inquiry: GM foods and application of the precautionary principle in Europe*, available at: http://nuffieldbioethics.org/wp-content/uploads/Submission_to_GM_inquiry_Nuffield_Council_on_Bioethics.pdf.

[407] Target Malaria advance its strategy on the strength of "the precedent that all successful malaria control programs to date have relied on attacking the mosquito vector rather than the parasite itself". This is persuasive without being convincing – we have remarked on the historic underfunding of Malaria research. [In the case of dengue, for example, the Eliminate Dengue programme, which uses a naturally occurring bacterium (Wolbachia) that reduces the ability of mosquitoes to pass dengue between people, is an alternative to Oxitec's vector control strategy. See: http://www.eliminatedengue.com/program.

[408] The *Cartagena Protocol*, for example, is risk focussed and does not explicitly take account of the benefits to human health of biotechnology use: "The Parties shall ensure that the development, handling, transport, use, transfer and release of any living modified organisms are undertaken in a manner that prevents or reduces the risks to biological diversity, taking also into account risks to human health." It is therefore silent on whether benefits to human health, for example, should be traded off against risks to the environment. See: https://bch.cbd.int/protocol/text/.

broadly before the technology is trialled.[409] The main issue with the phased approach is not the biosafety risks associated with well-designed and managed trials, but with the progressive closing down of the framing of successive questions, and the growth of technological momentum as experience of use and quantity of evidence increases.[410] Responsible innovation approaches that involve programmed break points and broader reflection at each stage have emerged to address this.[411]

6.32 The second point is that a precautionary approach must acknowledge uncertainties on all sides (those that relate to forbearance as well as different possible interventions), and take into account that different sets of consequences may be valued very differently by different people affected.[412] It should not, therefore, be restricted to a single dimension of scientifically measurable benefit or harm (e.g. harm to a defined human population in terms of projected morbidity or mortality), or to idealised experimental conditions.[413] A study by Sarah Hartley of the University of Nottingham, concerning the involvement of non-state actors in European risk assessment policy for genetically modified animals, supports the contention that "experts make decisions when policy-makers fail to acknowledge the limitations of science for risk decision-making."[414] Precautionary thinking involves the disciplined exercise of imagination, and the degree of uncertainty, which is necessarily related to the complexity of the system, demands proportionately broader engagement with the different interests that may be affected. This can only realistically be carried out in the context of a specified area of innovation, rather than abstractly in relation to a given

[409] The first is position was expressed by the House of Lords Science and Technology Select Committee in its report *Genetically modified insects* (2015), available at: http://www.publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/68.pdf (respectfully rejected in the subsequent government response) and in the response tour *Call for Evidence* by Target Malaria: "risk discussions.[…]. can only be effectively done when risk assessments can be carried out." Target Malaria envisage deployment within five to 10 years (from 2016) to allow safety and efficacy testing, and a full risk assessment. (The Chair of the Nuffield Council on Bioethics, Professor Jonathan Montgomery, gave oral evidence to the committee. Sir Roland Jackson, a member of the Council, also gave evidence in his capacity as executive Chair of Sciencewise.) It is also reflected in the concerns expressed in the NAS *Gene drives on the horizon* report that the Convention on Biological Diversity (CBD) is too precautionary and may inhibit gene drive research. It notes, with concern, that countries are now developing Cartagena-based regulatory systems "predicated on a strong precautionary, nearly preventative approach, which may restrict further gene drive research out of a precautionary concern about gene drives' intrinsic ability to spread and persist in the environment." National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and, at page 8.

[410] Even accumulating *unfavourable* evidence may contribute to the momentum, since the accumulation of evidence gives the technique a 'scientific basis', and generates 'scientific problems' that invite successive stages of research to address, compared with alternative (un-trialled) technology pathways that look increasingly 'speculative' or 'traditional' by contrast.

[411] Macnaghten P, Owen R, Stilgoe J. et al (2014) Responsible innovation across borders: Tensions, paradoxes and possibilities *Journal of Responsible Innovation* **1**(2): 191-9.

[412] The response to our *Call for Evidence* by EcoNexus, for example, contrasts precaution with risk-benefit analysis and points out uncertainty of most proposed potential benefits as well as what we know about DNA with what we know about the consequences of a DNA alteration in a 'total' sense. Their point is that possible benefits are usually – erroneously – presented as less uncertain than possible harms. They express concern about a mechanistic conceptual approach with "underlying assumptions that living organisms are basically machines that can be adjusted and refined as in mechanical engineering."

[413] "Possibly the claims today represent unbounded enthusiasm over the huge potential of gene drives. Then I ask those issuing promises to bear in mind the battle against malaria will take place under uncontrolled and uncontrollable conditions with sometimes uncooperative weather, logistical complications and just plain unforeseeable issues. We live in a world in which workers vaccinating children against polio have been assassinated. It can be a tough place to conduct field trials, too." Anonymous response to *Call for Evidence*.

[414] The concern, Hartley explains, "is not that the political is shaping the scientific, but that the scientific is shaping the political and in doing so masking political choices being made by scientific experts." Hartley S (2015) Policy masquerading as science: an examination of non-state actor involvement in European risk assessment policy for genetically modified animals *Journal of European Public Policy* **23**(2): 276-95, at page 290.The earlier contention was made in Millstone E, Van Zwanenberg P, Marris C, Levidow L, and Torgersen H (2004) *Science in trade disputes related to potential risks: comparative case studies*, European Commission technical report series, available at: http://ipts.jrc.ec.europa.eu/publications/pub.cfm?prs=1203.

technology.[415] Such reflection can help to illuminate the issues most relevant to the governance of innovation, which may not be those that are most apparent to the innovators.[416]

6.33 In framing the potential benefits and costs of particular technological strategies to address societal challenges, such as the infectious disease burden, it is generally accepted that a morally appropriate approach must have reference to the knowledge, interests and values of the local communities in affected areas. Engaging with such interests is usually thought to underwrite the innovators' 'social licence to practise'. Such dialogue is more effective when framed around challenges rather than specific technologies, partly because it helps to redress asymmetries of information between 'experts' and 'non-experts' (or experts of different kinds), and partly because it avoids the hypothecation of societal challenges to particular technological solutions and of technologies to particular societal challenges, thereby avoiding 'lock-in' at the level of public discourse.[417] Such procedures are, however, vulnerable to failure through, for example, lack of empowerment of local communities and of effectiveness of NGOs and other actors.[418] This may depend on the extent to which interested citizens are able (among other things) to frame questions and risks to be addressed, to participate directly in decisions, to make effective representations in the decision making process, to hold decision makers to account democratically and to have free access to rationales for decisions.[419] Political decision making is particularly vulnerable in areas with underdeveloped democratic systems.

6.34 A second question is the extent to which these procedures may be legitimately constrained or overridden by external considerations. This is particularly difficult where, for example, local population health priorities may be overridden in the interests of protecting biological diversity – or *vice versa*. This requires a disentangling of relationships, priorities, values and responsibilities between local, national, regional and global levels. Even where such a delicate disentangling can be accomplished a further concern must arise where fragile governance systems are pushed into crisis in emergency situations, such as those created by sudden outbreaks of epidemic disease.[420] It may be difficult, in such circumstances, to forestall urgent or precipitate action by governments who, understandably, put the immediate threats to the lives and health of their citizens ahead of concerns about biodiversity and the protection of world heritage.

Complexity and reversibility

6.35 A significant difficulty in predicting the effects of environmental release of gene drive systems is the complexity of the natural ecological context in which they are released (or to which they may spread). As noted above, 'ecological risk assessment', which aims to identify causal pathways and quantify the probability of different outcomes is only one input to responsible governance of innovation. As the complexity and uncertainty of the mechanism and outcomes increases, the

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[415] As Target Malaria made clear in their evidence it is necessary to assess "each application of this new technology on a case by case basis, considering the specific characteristics of each product developed, its intended use and conditions of use" to avoid oversimplification and generalisation. Target Malaria, responding to *Call for Evidence*.

[416] See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice, and the public good, available at:* http://nuffieldbioethics.org/project/emerging-biotechnologies/. These might include, for example, the different priorities given to different risks by potentially affected communities.

[417] On framing in relation to challenges, see response to *Call for Evidence* by BBSRC and MRC: "A Sciencewise-commissioned review of public dialogue on GM crops and food concluded that dialogue is more useful when challenges rather than technologies are discussed, e.g. how can we produce food sustainably?" (the review is available at: http://www.sciencewise-erc.org.uk/cms/assets/Uploads/Talking-about-GM.pdf). On hypothecation, see *Emerging biotechnologies* (op. cit.).

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

[419] Hartley S (2015) Policy masquerading as science: an examination of non-state actor involvement in European risk assessment policy for genetically modified animals *Journal of European Public Policy* **23**(2): 276-95; see also chapter entitled: "The treatment of social and ethical concerns in regulatory responses to agricultural biotechnology: an historical analysis" submitted in evidence as part of response to *Call for Evidence* by Sarah Hartley. Hartley surveys the literature on the involvement of non-state actors in risk management and the usurpation of decision making by experts, and uses Arnstein's 1969 ladder of citizen participation.

[420] Note, for example, calls for acceleration of work on modified mosquitoes to combat the outbreak of zika virus in Brazil ahead of the 2016 Rio Olympics: https://www.hhs.gov/about/news/2016/06/27/hhs-calls-center-innovation-accelerate-zika-vaccine-development.html and http://www.independent.co.uk/news/world/americas/zika-virus-president-obama-calls-for-rapid-development-of-tests-vaccines-and-treatments-to-combat-a6837511.html.

level of confidence in any such prospective assessment will become proportionately diminished. In such circumstances, the information supporting a deployment decision at any point will quickly become outdated; adaptive innovation, close monitoring, and the availability of controls and effective remedial interventions become proportionately more important than complex prior assessment models. A precautionary approach might seem to align with the epicurean-sounding principles such as that of causing the 'least possible degree of permanent perturbation' but, as this may depend on the complexity of the system as much as the magnitude of the intervention, it is not always clear what intervention would satisfy such a principle.[421]

6.36 A proposed technical mitigation against the risk of undesirable outcomes associated with the deployment of gene drive systems is the possibility of reversing them by introducing a second ('reversal') drive. In complex systems, there must be real concerns about whether this could undo or actually compound any environmental damage.[422] (Implicitly, it would also restore the original problem that it was designed to address.) This may be mitigated if success of the first drive were suggestive of a successful second drive; furthermore, restoring a trait once perceived as harmful would be justified if it were no longer harmful (for example, for disease vectors where the disease had been eradicated) or if the benefits were now thought to be outweighed by adverse effects.

Global justice and technology transfer

6.37 A very important set of issues arises when advanced biotechnologies that are developed in high income countries with an advanced research base will be used initially (or primarily) in low or middle income countries with significant internal inequalities of income or political power among citizens. The Nagoya Protocol was intended to redress the perceived unfairness of international bioprospecting and the exploitation of sovereign natural resources. The issue of 'benefit sharing' as construed by the Protocol, however, loses purchase on much of the biotechnology involved, whose development depends increasingly on computer-aided design rather than working with genetic resources.[423]

6.38 Concerns about international research and technology transfer are complex but have been raised in the past in relation to the behaviour of the pharmaceutical industry with regard to low income countries. These range from the exploitation of economically disadvantaged people as research participants, 'shopping around' among areas subject to lower or less well enforced standards of conduct ('regulatory arbitrage'), seeking advantageous deals with local authorities with inadequate political accountability, increasing technological or economic dependency on the donor countries, paternalism with regard to access to technology or technology options, creating unnecessary and inefficient 'high tech' solutions to problems for which less lucrative 'low tech' solutions are available, or, by seeking to empower communities, disrupting internal structures of

[421] "[…] for many diseases it is feasible to break the chain of transmission without permanently fracturing the backbone of the ecosystem genetic network. For example, precisely targeted tools like ONRAB or Raboral V-RG can control rabies without any genetic legacy effects by vaccinating wild animal reservoirs. Perhaps the least risky first deployments of genetically modified wild organisms might be to emulate the Oxitec strategy to modulate mosquito vector populations (http://www.oxitec.com/). Analogous to the sterile insect methods used in the past to interrupt pest reproduction, this approach could harness the potential of genetic methods to achieve specifically aimed impacts without permanently modifying the genetic information of the targeted population." Anonymous response to *Call for Evidence*.

[422] "These attempts to downplay concerns about potentially deleterious gene drive impacts are preposterous; the proffered solutions are cascading hypotheses, not bona fide remediation strategies." Anonymous response to *Call for Evidence*. It was also suggested in this response that the *Call for Evidence* should have included issues such as: "How will risk assessments for proposed gene drive releases be conducted and the corresponding results conveyed accurately to the general public and decision makers?" and whether it is "reasonable to believe we will be able to project all impending issues or detect unanticipated consequential changes that only emerge after extended periods in time to control or reverse them?" On overwriting drives see DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5 and Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[423] See, for example, Bagley MA (2015) *Digital DNA: the Nagoya protocol, intellectual property treaties, and synthetic biology*, Wilson Center Synthetic Biology project, available at: http://www.synbioproject.org/publications/digital-dna-nagoya-protocol/.

power or authority with unintended consequences.[424] This is not to say that research consortia and firms in the biotechnology and pharmaceutical sectors, as much as any other, are not striving to promote social wellbeing while either operating on a non-profit basis or making profits at a level that may be reasonable to compensate for the costs of innovation.[425] Nevertheless, what constitutes a 'benefit' for a particular community cannot simply be assumed in the absence of effective local political processes, and the acknowledgement of potential unintended or socially undesirable consequences may argue for new and more radical thinking about innovation systems, including pricing and IP policy.[426] Many researchers and companies, indeed, see their mission as both ethical and empowering for local communities.[427] Nevertheless, the extent to which local communities are empowered or enabled to benefit from imported biotechnologies, and the requirements that are needed to ensure that they are not disadvantaged even by well-meaning technology transfer, requires careful consideration that takes into account the social conditions, power structures and preferences of the communities concerned.

Other uses of CRISPR-enabled gene drives

6.39 Not all genome editing interventions may be to address an imminent public health or environmental threat. It is conceivable that genome editing may be contemplated to improve or enhance already safe environments, allowing the expression of human preferences over the composition of the biosphere, rather than addressing urgent needs. This raises the question of when, and under what conditions, particularly if there is an irreducible risk of harm, it might be appropriate to use biotechnologies to give expression to collective human preferences over and above meeting some commonly recognised need.

6.40 A further, and substantial set of concerns relates to the use of genome editing, particularly with gene drives, for malicious purposes, for example to trigger an ecological catastrophe. Such a use would at present require significant technical resources: although the use of CRISPR by amateurs has been reported, the creation of gene drives in such a context currently still seems beyond the ability of most amateurs.[428] Dual use potential of genome editing will be considered further in section 7.

Conclusion

6.41 The convergence of gene drive and genome editing technologies raises a range of concerns about biosafety and environmental release that are similar to those that have been raised about potentially hazardous biological research and genetically modified organisms. A major potential

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[424] On research in developing countries, see Nuffield Council on Bioethics (1999) *Genetically modified crops: the ethical and social issues* and *The use of GM crops in developing countries: a follow-up discussion paper* (2003), available at: http://nuffieldbioethics.org/project/gm-crops/. On high tech solutionism: see anonymous response to *Call for Evidence*: "Some proposed uses of gene drives appear to be high-tech solutions in search of problems." (The response cites dengue and lyme disease as having viable alternative solutions.)

[425] "while research capability might be predominantly in the hands of developed country laboratories, it can be argued that the most important and valuable benefits would be experienced by developing countries, with relatively little local investment. This situation changes the benefit sharing conversation, since typically the concern has been the exploitation of developing country resources for the benefit of developed countries. In a sense, the applications of gene drive approaches for malaria control could reverse the traditional benefit sharing equation." Response by Target Malaria to *Call for Evidence*.

[426] See Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, chapter 9; Pogge T, Rimmer M, and Rubinstein K (Editors) (2010) *Incentives for global public health: patent law and access to essential medicines* (Cambridge: Cambridge University Press).

[427] Target Malaria states that all its researchers have made "a 'global access' promise that specifies that the technology will be made available and accessible to developing world countries at an affordable price. In addition, the technology profile would provide equal access regardless of economic status, and would not require behavioural changes." Response to *Call for Evidence* by Target Malaria.

[428] Ledford H (2015) Biohackers gear up for genome editing *Nature* **524**(7566): 398-9. According to the Royal Society, "gene editing techniques are already widely used and similar to other areas of research there is the possibility of dual use of concern. Due to the speed of the development in the sciences, the decreasing costs and the increasing ease of use, the technological barriers to acquiring a biological weapon have been eroded. The skills and resources required remain considerable implying that it would likely require the backing of a nation state, however these barriers are likely to be rapidly eroded over the next few years with new technologies. […] the increased precision of gene editing technique also means that changes introduced may be effectively 'invisible', making forensic investigation and attribution difficult" (response to *Call for Evidence* by the Royal Society).

for benefit, as well as a major source of concern, is the use of genome editing systems with gene drives that are designed to spread a deliberate modification rapidly throughout a population in the interests of public health. Given the potential for suppression or amplification of effects owing to properties of ecological systems that are difficult to predict or to control, the environmental release of genome edited organisms when combined with gene drives needs to be approached with caution.

6.42 Precautionary approaches, while offering clear indications of principle are extremely difficult to give effect to through regulatory practice. The approach embodied in the *Cartagena Protocol*, which is being elaborated in local measures around the world, is not well suited to genome editing enabled by gene drive systems, which, if they work, may work in an escalating pattern until a population becomes saturated. Ecological risk assessment approaches may not be sufficiently well developed to inform decisions about gene drives; strategies to contain or mitigate are desirable, but those that rely on technical means to reverse the effects of the gene drive may not adequately address systemic effects and irreversibilities that follow from the initial deployment of the drive. The introduction of gene drives therefore requires flexible and adaptive models of innovation governance ('responsible innovation') that involve built-in opportunities for reflection and break points, and especially that avoid creating technological momentum around contingently preferred alternatives. Finally, particular attention needs to be given to issues of global justice in technology transfer from high-income countries to low- and middle-income countries.

6.43 The benefits of the responsible environmental release of genome-edited organisms could be significant and transformative, but the potential hazards are substantial and it is unlikely that the risk of unintended and undesirable consequences will be eliminated completely. This makes the political legitimacy of any decision especially important. Based on the experience with genetically modified mosquitoes to date, and the procedures required to bring conventional GMOs to market, and in the context of an existing and evolving international policy framework, it is likely to take a number of years before genome edited organisms are ready for large scale release into the wild. Well before then, the substantial ethical and societal questions identified above – including how the natural world and different states that human intervention may bring about are valued, of how to ensure that an intervention is just, of where the locus of different decisions should lie – will need to be addressed.

Section 7

Other applications

Section 7 – Other applications

Overview

Genome editing has potential applications in a range of settings, including energy and industrial production, military and even leisure applications, in addition to those covered in previous sections. Many of these involve the manipulation of microorganisms and aspire to rational design approaches characteristic of the field of synthetic biology.

The relationship between genome editing and synthetic biology is discussed and the enthusiastic uptake and development of genome editing tools among synthetic biology practitioners is noted. The interdisciplinary approach of much synthetic biology research, which integrates social and ethical reflection, is contrasted with models in other areas of research.

The value of genome editing in developing the bioeconomy is discussed, as are areas in which genome editing may accelerate or facilitate industrial production using microorganisms. The ease of use of CRISPR-Cas9 alongside or outside institutional settings (in organised competitions, or for community or private research, or for artistic and cultural purposes) is discussed. A range of biosafety measures are noted and the question of the criteria according to which they should be engaged recurs.

Applications of genome editing of potential interest to the military are enumerated although the difficulty of researching this area is highlighted. A number of biotechnology-related initiatives in the UK and US defence communities are outlined and the implication of genome editing in these is noted. Biosecurity and potential dual use issues are noted, and differences in perspective between the security and scientific communities, and between the UK and US, are identified.

A number of moral and societal questions are identified, including the difficulty of applying conventional regulatory mechanisms based on institutional membership, market regulation, cost or knowledge barriers.

Introduction

7.1 Genome editing systems have applications across biology, including plants, animals and humans, but the most promising system currently, CRISPR-Cas9, is based on a viral defence mechanism endogenous to bacteria.[429] Bacteria are ubiquitous and represent some of the simplest forms of cellular life.[430] The bacterial biomass may well outweigh the combined mass of all plants and animals on earth.[431] Microorganisms, through which the rest of the biosphere is connected to the non-biological environment through uptake and conversion of energy and chemicals that support life, are fundamental to life on earth.[432] (For example, the community of bacteria in the gut – the gut microbiome – is necessary for digestion of food and its composition is increasingly linked to disease predisposition.[433] The energy-generating organelles in eukaryotic cells, mitochondria, and the photosynthetic organelles of plants, chloroplasts, are thought to be derived from bacteria that were incorporated at an early phase of plant and animal evolution.[434]) The plasticity of microorganisms and their ability to adapt to environmental challenges through rapid genome evolution, makes them both useful as potential sources of chemical compounds but also potentially harmful (pathogenic).[435]

7.2 Genome editing is a potentially valuable tool in industrial biotechnology, further transforming manufacturing processes, generating new products, reducing pollution, improving resource

[429] Doudna JA and Charpentier E (2014) The new frontier of genome engineering with CRISPR-Cas9 *Science* **346**(6213), doi: 10.1126/science.1258096; Charpentier E (2015) CRISPR-Cas9: how research on a bacterial RNA-guided mechanism opened new perspectives in biotechnology and biomedicine *EMBO Molecular Medicine* **7**(4): 363-5.
[430] Bacteria comprise the kingdom that includes eubacteria and cyanobacteria. See also Cavalier-Smith T (1998) A revised six-kingdom system of life *Biological Reviews* **73**(3): 203-66.
[431] Whitman WB, Coleman DC and Wiebe WJ (1998) Prokaryotes: the unseen majority *Proceedings of the National Academy of Sciences* **95**(12): 6578-83.
[432] Microorganisms include bacteria, archaea, protozoa, algae, fungi, and viruses.
[433] Cho I and Blaser MJ (2012) The human microbiome: at the interface of health and disease *Nature Reviews Genetics* **13**(4): 260-70.
[434] Pennisi E (2014) Modern symbionts inside cells mimic organelle evolution *Science* **346**(6209): 532-3.
[435] For example, bacteria have been used to produce plastics, see: Urtuvia V, Villegas P, González M, and Seeger M (2014) Bacterial production of the biodegradable plastics polyhydroxyalkanoates *International Journal of Biological Macromolecules* **70**: 208-13.

conservation and reducing costs when combined with other enabling technologies such as DNA synthesis, microarray analysis, next-generation DNA sequencing, programmable DNA-binding proteins, and 'cell factories'. This is achieved by re-engineering metabolic pathways: the series of chemical reactions, controlled by enzymes, by which cells convert relatively low-cost or toxic inputs into valuable metabolic outputs, such as fuels, high-value chemicals, materials and pharmaceuticals. The particular value of genome editing lies in its potential to facilitate multiple changes necessary to modify a metabolic pathway so that it can work efficiently in this way.[436] Applications, however, are not limited to the aims of industrial biotechnology and are of interest to a range of other users operating outside the research fields and institutions that have been considered so far in this report.

Genome editing and synthetic biology

7.3 The design and construction of novel artificial pathways, organisms or devices utilising biological materials, or the adaptation of biological systems for a specified purpose describes the field of synthetic biology. This field has developed a distinct identity through the pursuit of defined aims and the adoption of characteristic practices. The aims of synthetic biology comprise the rational design of biological systems according to engineering principles, drawing on disciplines of molecular biology, computer science, chemistry and engineering.[437] For its practitioners, these features make synthetic biology conceptually distinct from earlier forms of genetic engineering, such as the development of transgenic plants.

7.4 From the point of view of synthetic biologists, genome editing introduces a valuable new set of tools that can be used to modify or design genetic sequences at the level of individual base pairs and, potentially, at multiple sites in a given gene or genome.[438] It allows them to test a number of designs or to use the single design-build-test cycle preferred by many synthetic biologists.[439] The techniques of genome editing have been enthusiastically embraced by synthetic biologists as Cas9 allows the prolific creation of DNA-binding proteins, and many synthetic biologists are involved in engineering variants of Cas9.[440] The orthogonal nature (independence) and programmability of the sgRNA/CRISPR-Cas9 pair leads to the possibility of building larger genetic circuits using greater numbers of synthetic regulatory proteins linked to Cas9.[441]

7.5 Synthetic biologists are self-consciously elaborating a novel field. They see the field as transforming biology as a practical discipline, not only in relation to the adoption of technical innovations, but also epistemically and institutionally (breaking down disciplinary barriers and re-imagining biology as an engineering discipline), and socially and politically (e.g. the desire to build a community and to inculcate certain norms, including those of open source publication and responsible innovation practices).[442] While, undoubtedly, genome editing has given a fillip to synthetic biology it does not, however, seem to have the same rhetorical significance here as in

[436] Response to *Call for Evidence* by the Royal Society.
[437] Cameron DE, Bashor CJ and Collins JJ (2014) A brief history of synthetic biology *Nature Reviews Microbiology* **12**(5): 381-90.
[438] See, for example, Nielsen AAK and Voigt CA (2014) Multi-input CRISPR/Cas genetic circuits that interface host regulatory networks *Molecular Systems Biology* **10**(11): 763.
[439] Response to *Call for Evidence* by the Royal Society.
[440] Puchta H (2016) Genome engineering using CRISPR/Cas: getting more versatile and more precise at the same time *Genome Biology* **17**:51; "Genome editing is a tool which is an accelerator and catalyzer of synthetic biology approaches wherever microorganisms are involved. Genome engineering IS a part of synthetic biology. It is at the very definition of synthetic biology, and discussions about genome editing are directly relevant to synthetic biology" (response to *Call for Evidence*, anonymous).
[441] *CRISPR meets synthetic biology: a conversation with MIT's Christopher Voigt*, available at: http://blog.addgene.org/crispr-meets-synthetic-biology-a-conversation-with-mits-christopher-voigt.
[442] In general see: Schyfter P, Frow E and Calvert J (2013) Synthetic biology: making biology into an engineering discipline *Engineering Studies* **5**(1): 1-5; for epistemic distinctness and relation to systems biology, see Nordmann A (2015) Synthetic biology at the limits of science, in *Synthetic biology: character and impact*, Giese B, Pade C, Wigger H and von Gleich A (Editors), (Cham: Springer), pp 31-58; for an assessment of how far the ideals of synthetic biologists are achieved in practice, see Mercer DW (2015) 'iDentity' and governance in synthetic biology: norms and counter norms in the 'international genetically engineered machine' (iGEM) competition *Macquarie Law Journal* **15**: 83-103.

other areas of biology.[443] This might be partly attributable to the fact that the natural reservoir of metaphor for synthetic biology is technical (engineering, construction) rather than textual (editing).[444]

7.6 Synthetic biology does, however, offer an insight into possible ways of approaching genome editing as an innovation within research and industry that is essentially different to the translational approaches of biomedicine or, again, public health innovations. Owing, in part, to the different cultures that are integral to synthetic biology (e.g. that of computer science) and in part to lessons about innovation learned from the observation of other fields (e.g. nanotechnology), it has been common for synthetic biologists to adopt responsible innovation practices from the outset.[445] These tend to see ethical reflection and social engagement as longitudinally integral to their practice ('ethical by design'), as both guiding and governing research, rather than as challenges or decisions to be addressed at particular stages.[446]

Industrial applications

7.7 The enthusiasm for genome editing in biotechnology can be understood in the light of its potential value in developing the bioeconomy – those parts of the economy that use renewable biological resources to produce food, materials and energy – especially in replacing depleted or polluting resources such as fossil fuels.[447] The main industrial applications of genome editing are in the production of simple chemicals or proteins.[448] Microorganisms have greater genomic plasticity than larger organisms and are easier to engineer. Specific alterations to the genomes of bacteria such as *Escherichia coli* result in changes to metabolic pathways such that they can produce chemicals and proteins that may not be efficiently obtained otherwise through processes such as fermentation. Chemicals include hydrocarbons such as butanol and propane that can replace fossil fuels and petrochemicals.[449] They also include food additives and flavourings.[450] Proteins include bioactive antibody segments; for example, *Actinomycetales* is a bacterial order that includes the soil bacteria, *Streptomyces* spp, whose members have the capacity to produce a variety of medically and industrially relevant secondary metabolites: antibiotics, herbicides, chemotherapeutics, and immunosuppressants, such as vancomycin, bialaphos, doxorubicin and rapamycin.[451]

7.8 One kind of application – again an objective of earlier genetic engineering – is to use modified plants, such as the tobacco plant, or domestic animals (cows, sheep, goats) as biological factories to produce vaccines or other pharmaceutical compounds ('pharming').[452] These methods of vaccine production may have significant advantages in terms of speed and low cost over production methods that involve growing vaccines in hen's eggs. These advantages could be

[443] "Accurate circuit design and metabolic pathway engineering are synthetic biology aims: by providing 'designer nucleases' for engineering (alongside current highly advanced DNA synthesis capabilities), GE has enabled precision engineering of cells with novel pathways and properties. Potential end-points would be those envisaged for synthetic biology", response to *Call for Evidence* by BBSRC and MRC.

[444] We are grateful to Jane Calvert of the University of Edinburgh (and a member of our earlier Emerging Biotechnologies Working Party) for information about synthetic biology and the observation about the different lexicons.

[445] On responsible innovation see Stilgoe J, Owen R, and Macnaghten P (2013) Developing a framework for responsible innovation *Research Policy* **42**(9): 1568-80. These can be seen reflected to a certain extent in the UK's *Synthetic biology roadmap* (2012), available at: https://connect.innovateuk.org/documents/2826135/3815409/Synthetic+Biology+Roadmap+-+Report.pdf/fa8a1e8e-cbf4-4464-87ce-b3b033f04eaa.

[446] See, for example, http://www.synbio.ed.ac.uk/responsible-research-and-innovation.

[447] For 'bioeconomy' see https://ec.europa.eu/research/bioeconomy/index.cfm. See also response to *Call for Evidence* by Vlaams Instituut voor Biotechnologie: "It should not be underestimated how many applications of genome editing in micro-organisms can be foreseen. And these will have a wide variety of applications in (veterinary) medicine, food and feed and industrial applications (the bio-based economy)."

[448] See, for example, https://amyris.com/.

[449] Kallio P, Pásztor A, Thiel K, Akhtar MK and Jones PR (2014) An engineered pathway for the biosynthesis of renewable propane *Nature Communications* **5**: 4731.

[450] See, for example, http://oxfordbiotrans.com/products/.

[451] Tong Y, Charusanti P, Zhang L, Weber T and Lee SY (2015) CRISPR-Cas9 based engineering of actinomycetal genomes *ACS Synthetic Biology* **4**(9): 1020-9.

[452] Shinmyo A and Kato K (2010) Molecular farming: production of drugs and vaccines in higher plants *Journal of Antibiotics* **63**(8): 431-3.

particularly significant in emergency situations where there is a strong incentive for swift vaccine development and translation into rapid, large-scale production.[453]

7.9 A benefit of using engineered microorganisms in the production process is the potential to use inexpensive feedstocks, in some cases waste products from other processes or settings, or even just to manage and degrade waste.[454] These are becoming particularly important applications as environmental protection, mitigation and remediation become more significant policy objectives.[455]

Non-institutional applications

7.10 One outgrowth of synthetic biology is the annual international Genetically Engineered Machine (iGEM) competition, which is contested by groups of undergraduate, high school and graduate students.[456] Each group is supplied with a standard distribution kit and encouraged to design and build genetically engineered systems using standard biological parts (BioBricks).[457] The competition has a serious purpose: many successful entries advance research in the field and some go on to form start-up companies as a result.[458] Since 2014 all iGEM BioBrick distribution kits that are sent to registered competitors have contained CRISPR-Cas9 components.[459]

7.11 The comparatively low cost and ease of use of the CRISPR-Cas9 system has made it feasible for a greater range of users, beyond those who would ordinarily make use of the techniques of molecular biology. These include those whose purpose is not institutionally-sponsored academic or commercial research: DIY or 'garage' biologists, 'biohackers', and enthusiastic amateurs who are either interested in learning about or experiencing microbiological techniques, carrying out informal research, or making biological products. This prospect has been greeted variously with enthusiasm, cynicism and concern.[460] A number of sites providing laboratory and ancillary services for amateur microbiologists have sprung up to support the widening interest in microbiology.[461] It is, however, also possible for individuals to pursue this interest in private homes using kits and reagents that are available to order online.[462] Companies have been established to serve this interest: in 2016 a DIY Bacterial CRISPR kit to render *E. coli* resistant to streptomycin, an antibiotic that is in clinical use, can be obtained for UD$140 dollars.[463]

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

[454] "Hypothetically (for example) one could engineer microorganisms to take the CO_2 out of the atmosphere to make carbon-based biofuels which will then release the same amount of CO_2 (but not more) when consumed." (anonymous response to *Call for Evidence*).

[455] Response to *Call for Evidence* by the Royal Society of Biology.

[456] http://igem.org/Main_Page.

[457] http://parts.igem.org/Help:An_Introduction_to_BioBricks.

[458] http://igem.org/IGEM_Startups.

[459] See: http://parts.igem.org/CRISPR.

[460] "There is an emerging movement in which people are setting up shops in their garages. Community labs are being set up that allow anyone to come in and be trained. Previously, you had to be an expert in making zinc-finger vectors to edit DNA, but now — because CRISPR-Cas systems are so easy to use — anyone with molecular biology training can do it. On the one hand it is an exciting time for the field because this movement is going to bring in a lot of new ideas and talent. But on the other, it is also going to create new regulatory questions. The democratization of biological engineering is inevitable. Now we have to size up the risks and benefits so we can harness what is going to come of it." Interview with Tim Lu from MIT, Tauxe W (2015) Q&A: Tim Lu. Cocktail maker *Nature* **528**(7580): S14. On bio-optimism and bio-pessimism, see Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, chapter 1.

[461] The first and perhaps best known of these is Silicon Valley's BioCurious (see: http://biocurious.org/). London has Biohackspace (see: https://biohackspace.org/). See also Ledford H (2015) Biohackers gear up for genome editing *Nature* **524**(7566): 398-9.

[462] Research interview with professors Drew and Hewinson from APHA.

[463] Users of the kit would, however, require additional standard laboratory hardware, which would raise the price of setting up the experiments significantly, if not prohibitively, for the private market. See: http://www.the-odin.com/diy-bacterial-crispr-kit/ (price as advertised in August 2016).

7.12 CRISPR has also been identified as both a possible theme and a medium of expression and cultural intervention for artists and other cultural actors. The late twentieth century saw the rise of bio-art and bio-activism, with practitioners using the techniques and materials of the life sciences to create art and political commentary. Pioneers included Eduardo Kac, Joe Davis, and Marta de Menezes.[464] Older bioart laboratories such as the University of Western Australia's Symbiotic A have been joined in the twenty-first century by public-orientated laboratory spaces such as California's BioCurious, or the C-LAB art collective. While some bioart has itself been critiqued (for example, the controversy surrounding Kac's green fluorescent rabbit – 'GFP Bunny' – and the suggestion that he was exploiting animals for non-essential purposes), both bioart and the so-called DIYBio citizen science movement have interacted with several research communities and some sectors of the art community as a source of critique of and creative expression within biotechnology.[465] Common themes include the democratisation of science, drawing attention to dual use, biosecurity, and biological warfare, critiquing the commodification and manipulation of life under neoliberal capitalism, and highlighting eugenic and environmental concerns, as well as more aesthetic and design-centred uses of the techniques of biotech. Bioartists and activists are already interested in the new generation of easy-to-access genome editing tools for creative and political expression.

7.13 While it is in the interests of the public to encourage creative and critical engagement with science and technology, given the latter is a major component of contemporary knowledge economies, the perceived potential for inadvertent harm or misuse has heightened concern about whether some techniques should not be freely available outside regulated institutional and/or biomedical contexts. Currently, European DIYBio is considered to be better or more consistently regulated than its US counterpart but there is wide recognition that new genome editing techniques may well be game-changing in their ability to enable of non-institutional actors.[466]

Biosafety

7.14 Genetically altered organisms present a theoretical risk of harm to those handling them and, if they escape or are released from laboratories and controlled environments, to other people and to natural ecosystems. Where these organisms are classified as 'genetically modified' there are multiple levels of 'biosafety' regulation relating to handling and releasing them.[467] Health and safety regulations cover the safety of those working with genetically modified microorganisms (GMMs) and 'larger genetically modified organisms' (GMOs), including any GMOs that pose a significant risk. In the UK, for example, the Genetically Modified Organisms (Contained Use) Regulations 2014 provide for human health and safety, and environmental protection, from GMMs in contained use, as well as human health and safety from GMOs including animals, plants and insects.[468] Compliance with these Regulations is overseen by the Health and Safety Executive and its inspectorate.[469] There is cause for greater concern, however, in countries with less well developed infrastructures, where there may nevertheless be significant research funding, where the kits are easily available and many PhD students use them. We heard in evidence claims that the biosafety and biosecurity facilities in some countries can be generally quite poor: the tools

[464] Yetisen AK, Davis J, Coskun AF, Church GM and Yun SH (2015) Bioart *Trends in Biotechnology* **33**(12): 724-34.
[465] Myers W (2015) *Bio art: altered realities* (London: Thames and Hudson).
[466] See Seyfried G, Pei L and Schmidt M (2014) European do-it-yourself (DIY) biology: beyond the hope, hype and horror *BioEssays* **36**(6): 548-51.
[467] The term 'genetically altered organisms' is used in the preceding sentence to avoid the legal term 'genetically modified organism'; organisms that have been subject to genome editing may fall within or outside the scope of the legal definition of 'genetically modified organism'. For a discussion of the significance of this distinction, see section 5.
[468] The Regulations transpose and implement European Council Directive 2009/41/EC on the contained use of genetically modified micro-organisms and (unlike the Directive), also cover larger GMOs (animals, plants and insects). See: http://www.hse.gov.uk/pubns/books/l29.htm.
[469] Other elements of the patchwork of health and safety legislation are also relevant to the use of GMOs, including the general requirements of the Health and Safety at Work Act 1974 and associated regulations, and the Control of Substances Hazardous to Health Regulations 2002. The Scientific Advisory Committee on Genetic Modification (SAGCM), an advisory body of the Health and Safety Executive, issues guidance on good practice (prepared in consultation with the Health and Safety Executive) and health and safety inspectors may refer to this in seeking to secure compliance with the law.

might be used inappropriately on an open bench, scientists might become infected, and pathogens may be released.[470]

7.15 Transport of genetically modified or potentially hazardous organisms is also covered by legislation that places controls on certain movements and labelling.[471] The Cartagena Protocol is specifically orientated towards technology transfer, providing a mechanism for lower income countries to assert a range of considerations such as public health, economic and environmental benefits and costs when controlling imports of living modified organisms produced by biotechnology.

7.16 The release of GMMs and GMOs are covered by national laws and regulations, although principles of environmental protection are given consistency by responsibilities under the Convention on Biological Diversity, and most countries adopt similar procedures including for scientific risk assessments. Regional agreements are particularly important because the spread of genetically altered populations does not respect national borders *per se*.[472]

Martial applications

7.17 As with other biotechnologies there is a potential for military interest in genome editing, although the nature and level of the interest, and of any actual resourcing, is notoriously hard to research due to its secretive nature.[473] Areas of potential interest include research aimed at improving battlefield medicine and the acceleration of basic research into physiological and psychological responses to trauma, healing mechanisms and the development of related products and treatments. More speculatively, there is also potential interest in employing genome editing for the enhancement of personnel, in relation to genetic susceptibilities to conditions that they might experience in warfare, improving concentration, and other physiological characteristics such as physical fitness. The most evident security interest, however, is in identifying and countering external threats.

7.18 In the UK, the basic biological research that might generate applications of interest to the military and security agencies is funded by the Medical Research Council (MRC) and Department of Health. The Ministry of Defence (MoD) research budget (officially in the range of £400M in 2015/16) is spent almost entirely on applied research. This supports the MoD Defence Science and Technology Laboratory (DSTL), as well as public-private collaborations and R&D in the private sector.[474] The DSTL runs a human sciences programme, with projects focussed on defence personnel, and a chemical, biological and radiological programme, which, among other things, investigates medical counter-measures to chemical and biological agents ranging from

[470] Research interview with Professors Drew and Hewinson (APHA). It should be borne in mind that research organisms, as we stated in section 6, are often ideal for research (inbred etc.) but not robust in wild environments as a consequence – the issue here is animals that are edited for release into the wild.

[471] In the UK it is also covered by a variety of legislation applying to the carriage of dangerous goods (the Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009 and the *Accord européen relatif au transport international des marchandises dangereuses par route*, known as ADR) as well as Regulation (EC) 1946/2003 on transboundary movements of GMOs.

[472] In the EU these include Directive 2001/18/EC on the deliberate release of GMOs into the environment which covers microorganisms when they are not covered by Directive 2009/41/EC on contained use of genetically modified micro-organisms. In the UK, measures are implemented through a sheaf of regulations under the Environmental Protection Act 1990 including the Genetically Modified Organisms (Risk assessment) (Records and Exemptions) Regulations 1996 and The Genetically Modified Organisms (Deliberate Release and Risk Assessment-Amendment) Regulations 1997. Deliberate releases of genetically modified organisms come under the responsibility of The Department for Environment Food and Rural Affairs (DEFRA) England, with Scottish and Welsh Governments being responsible for deliberate releases of GMOs in their respective jurisdictions.

[473] We invited senior representatives from the UK Ministry of Defence to participate in a research interview in support of this project but, after informal discussions, this was not taken forward. The difficulty of researching military funding on biotechnologies, and the difficulties that creates for public decision making, is noted in the Council's report on *Emerging Biotechnologies*; see also independent research commissioned to support that project.

[474] See: https://www.gov.uk/government/organisations/defence-science-and-technology-laboratory.

vaccines to protect personnel against infection, to post-exposure treatments.[475] While genome editing may have many hypothetical uses in military contexts, the official literature is of a very vague and general nature, and what these programmes actually involve cannot accurately be inferred with confidence. Nevertheless the National Security Strategy and Strategic Defence and Security Review 2015 acknowledges the 'huge potential' of advances in medical technology, genetic engineering and biotechnology (among other fields, and to which genome editing is arguably now intrinsic) for national security and prosperity.[476] It also accepts as a fact that controls on access to knowledge and materials will become harder to maintain leading to these technologies becoming available to more state and non-state actors, including terrorists, and organised crime groups. This is explained as a consequence of a reduction of Western states' 'technological advantage' over other actors.[477] Consequently, there is sensitivity to the emergence of new security threats and an acknowledgement of the need for effective horizon scanning. (The National Security Strategy and Strategic Defence and Security Review 2015 also mentions a new 'cross-government Emerging Technology and Innovation Analysis Cell' which will support 'scouting for new threats', although this is not more specific than identifying biotechnology as a risk area.[478])

7.19 In the US, the Defense Advanced Research Projects Agency (DARPA) is a major funder of science research (its overall budget for the 2016 fiscal year is officially US$2.97 billion) and has a dedicated Biological Technologies Office, which exists to exploit the intersection between biology and the physical sciences.[479] A number of the projects it funds are in the field of synthetic biology and these may be expected to be optimised through the use of genome editing. These projects are typically ambitious and expensive. They include the 'living foundries' project, the aim of which is "to create a revolutionary, biologically-based manufacturing platform to provide new materials, capabilities, and manufacturing paradigms for the DoD [Department of Defense] and the Nation", Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) which aims "to develop and exploit synthetic biology for the in vivo creation of nucleic acid circuits that continuously and autonomously sense and respond to changes in physiologic state and for novel methods to target delivery, enhance immunogenicity, or control activity of vaccines, potentially eliminating the time to manufacture a vaccine ex vivo", and Biological Robustness in Complex Settings (BRICS), a translational project based on the 'living foundries' to "leverage newly developed technologies for engineering biology towards enabling radical new approaches to solving National Security challenges". In the US, especially since 11 September 2001, national security applications appear to be a trump card among impact statements for research funding.

Biosecurity and dual use

7.20 Much of the military research and military horizon scanning, to which genome editing is potentially relevant and for which public information is available, is concerned with imagining and preparing for the offensive actions that a notional adversary might initiate. Such actions might involve, for example, aggressors obtaining pathogens for deployment against an enemy or civilian population. Biosecurity measures, including controls on access to and use of certain reagents, and monitoring and auditing research, are intended to address such possibilities.[480] Our evidence collection

[475] For the human sciences programme, see https://www.gov.uk/government/publications/human-and-medical-sciences-project-portfolio; for the Chemical, Biological and Radiological programme, see: https://www.gov.uk/government/publications/chemical-biological-and-radiological-programme.

[493] See: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/478933/52309_Cm_9161_NSS_SD_Review_web_only.pdf.

[477] *National security strategy and strategic defence and security review* (2015), op.cit. UK Universities are now legally obliged to have in place a 'PREVENT' strategy to identify individuals at risk of being radicalised or of inciting radicalisation.

[478] Ibid.

[479] For DARPA programme budget see: http://www.darpa.mil/attachments/(2G1)%20Global%20Nav%20-%20About%20Us%20-%20Budget%20-%20Budget%20Entries%20-%20FY2016%20(Approved).pdf. This includes $389M on basic research, $1.2 Bn on applied research and $1.3 Bn on 'advanced technology development').

[480] Professor Drew said that a major risk was that as an international reference laboratory, APHA may supply reagents for one purpose that are subsequently used for a different purpose. He said that APHA only ever supply reagents to national laboratories and that they are imported only with a licence of the Government of that country, and the APHA ensure that the laboratory is accredited to the biocontainment level appropriate to the pathogen.

revealed concerns that these measures may need to be enhanced since, while the supply of pathogens is carefully regulated, the supply of materials that are needed to manipulate them is not and it is hard for authorities to monitor these activities.[481] In the US, DARPA has launched a project called 'Improv' which involves a call to technologists for designs for possible military technologies built exclusively from repurposed software, computer code, and materials that are available to the general public. The aim is to demonstrate the ease with which available resources can be repurposed to present a security risk and to identify likely pathways.[482] As genome editing systems become available on the open market, their repurposing may become an increasing theoretical source of concern.[483]

7.21 As well as obtaining materiel that can be deployed to cause a security threat, potential aggressors might make use of knowledge from research for offensive purposes. Research that has both civilian and military (or terrorist) uses is known as 'dual use' research. The possibility of dual use presents a dilemma: should potentially beneficial research be encouraged in the knowledge that this entails a risk of such knowledge being misused, or should the benefits be foresworn in an attempt to avoid running such a risk? The usual response is not to run towards one horn or the other of this dilemma, although there is often a tension between the security community, with its culture of containment, and the scientific community, which depends on sharing research findings as its lifeblood. The response is usually premised on the expectation that progress in knowledge production may be diverted but cannot ultimately be dammed, and it is therefore preferable for responsible scientists to be at the forefront of research. This, however, may imply the reluctant acceptance of an 'arms race' between measures and countermeasures, that entails a necessary tolerance for certain intrusions and limitations on research.[484]

7.22 Since it is possible to imagine malicious use for the results of almost all (biological) research, a special subclass of research that, "based on current understanding, can be reasonably anticipated to provide knowledge, products or technologies that could be directly misapplied by others to pose a threat to public health and safety" (known as 'dual use research of concern' – DURC) has been proposed.[485] The seminal report addressing the dual use dilemma is the US National Academies of Sciences 2004 report, *Biotechnology research in an age of terrorism* (known as the 'Fink Report' after its chair, MIT biologist, Gerald Fink). Developing the classification in the Fink report, the US National Science Advisory Board for Biosecurity identified seven categories of knowledge, products or technologies arising from life sciences research that

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[481] Research Interview with professors Drew and Hewinson (APHA). It was observed that someone in the UK might be able to obtain from abroad materials to conduct gain of function experiments and that this would be difficult to detect or monitor.

[482] See: http://www.darpa.mil/news-events/2016-03-11.

[483] The question of vetting customers for genome editing kits was raised at a roundtable on biosecurity and genome editing held in July 2015 where industry representatives were reassuring that they would only provide kits to bona fide researchers (which may include biohackers supported by a reputable institution). (Bioseccu.re, who hosted the meeting, note that a briefing on the interaction between genome editing technologies and the Biological Weapons Convention will be prepared for the treaty's forthcoming 8th Review Conference in 2016 – see: http://biosecu.re/biosecure/writing/Entries/2016/5/7_Gene_editing%2C_bioweapons_%26_(inter)national_security.html. However, one of our research interviews suggested that this was not always the case and that bona fides customer may not always need to be demonstrated and the use to be made of the kits is not always clear to the supplier. (Research interview with APHA).

[484] Research carried out under the aegis of the UK's Animal and Plant Health Agency (APHA), for example, manages the possibility of dual use by weighing benefits and risks at the outset, during the life of the project and at publication, and the agency has the option of retaining that information and ensuring that it is not made public. (Research interview with Professors Drew and Hewinson of APHA).

[485] "Uses of biological technologies and organisms in warfare have waned since the Second World War, likely because biology is stochastic and difficult to control. Nevertheless, all of the microorganisms, animal, and human applications of gene modification technologies are likely to be relevant in military and security contexts," response to *Call for Evidence* by Angel Petropanagos and Carlos Mariscal. On DURC, see: National Science Advisory Board for Biosecurity (2007) *Proposed framework for the oversight of dual-use life sciences research:* strategies for minimizing the potential misuse of research information, available at: http://osp.od.nih.gov/office-biotechnology-activities/nsabb-reports-and-recommendations/proposed-framework-oversight-dual-use-life-sciences-research. See also: Nuffield Council on Bioethics background paper, *Dual use in biology and biomedicine*, prepared by Filippa Lentzos (2015), available at: http://nuffieldbioethics.org/wp-content/uploads/Background-paper-2016-Dual-use.pdf.

would indicate a potential for dual use of concern.[486] Such concerns are addressed through a range of policy measures, such as, in the UK, the joint BBSRC, MRC and Wellcome Trust policy on managing risks of research misuse, that is intended to heighten awareness of risks and is designed to dovetail with the research and institutional governance, and measures to improve the education of researchers about biosecurity and dual use potential.[487]

Box 7.1: Gain-of-function research

A particular source of dual use concern is gain-of-function (GoF) research, such as research into increasing the virulence of disease agents. A frequently cited example is the case of Australian researchers Ronald Jackson and Ian Ramshaw who, in 2001, published a jointly-authored paper exploring the potential control of mice, a major pest in Australia, by infecting them with an altered mousepox virus that would cause infertility. The researchers used a genetic engineering technique to insert the gene for interleukin-4 (IL-4) into the mousepox virus. They found, however that the altered virus had the capacity to kill both mice that were naturally resistant to the ordinary mousepox virus and those that had been vaccinated against it. Publication of their findings in the *Journal of Virology* was followed by complaints that they had provided sensitive information that could lead to the manufacture of biological weapons to potential terrorists who might use the knowledge to create vaccine resistant strains of other pox viruses, such as smallpox, that could affect humans.[488]

Similar controversy surrounded the research into H5N1 flu virus by separate groups in the US and the Netherlands in 2011. This research found that a small number of genetic alterations could enable mammal-to-mammal transmission of the virus by aerosol. Publication was delayed – both research groups agreeing to a voluntary postponement – while security experts and biologists debated the virtues of publishing or suppressing the research. Although no clear consensus was reached, highlighting the different concerns motivating the biological research and security communities, modified versions of both papers were eventually published.[489]

7.23 Genome editing has been discussed in the context of a 2015 international inter-academy meeting in preparation for the 2016 8th Review Conference of the Biological and Toxin Weapons Convention (BWC).[490] The inter-academy meeting report mentions genome editing among developments in science and technology posing future risks for the BWC as a potential means of developing novel agents.[491] From this, a number of areas have been elaborated:

- the use of gene editing tools to produce novel pathogens and/or alter entire populations;
- reduction of risk by removing potential agents from naturally occurring crops e.g. removing the ricin gene from the castor oil plant *Ricinus communis*;
- the difficulty of distinguishing between a 'natural' and 'unnatural' disease outbreak;
- the lack of 'fingerprints' from the use of gene editing techniques may hamper forensic investigations;

[486] These are knowledge, products or technologies that would: (1) enhance the harmful consequences of a biological agent or toxin; (2) disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification; (3) confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate their ability to evade detection methodologies; (4) increase the stability, transmissibility, or the ability to disseminate a biological agent or toxin; (5) alter the host range or tropism of a biological agent or toxin; (6) enhance the susceptibility of a host population; and (7) generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent. See: United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (2014), available at: http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf; National Research Council (2004) *Biotechnology research in an age of terrorism* (2004), available at: https://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism.

[487] See: *BBSRC, MRC and Wellcome Trust position statement on dual use research of concern and research misuse* (2015), available at: https://wellcome.ac.uk/funding/managing-grant/managing-risks-research-misuse.

[488] Jackson RJ, Ramsay AJ, Christensen CD, *et al*. (2001) Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox *Journal of Virology* **75**(3): 1205-10. For their reflections on the ensuing furore, see: The mousepox experience (2010) *EMBO reports* **11**(1): 18-24.

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

[490] Inter-academy partnership (2015) *The Biological and Toxin Weapons Convention: implications of advances in science and technology*, available at: https://royalsociety.org/topics-policy/projects/biological-toxin-weapons-convention/.

[491] The transformative potential of advances in life sciences were highlighted in 2014 by the Spiez CONVERGENCE, a foresight workshop series on advances in the chemical and biological sciences and their interaction, of relevance to the Chemical Weapons Convention and the BWC: "The life sciences are advancing at an unprecedented pace, and the amount of data and knowledge acquired is such that non-linear leaps in science and technology should be expected which could lead to a genuine sea change. The wide and rapid impact that the removal of a single obstacle can have, became apparent during the workshop when the use of CRISPR/Cas in genomic editing was discussed." Spiez Laboratory, the Swiss Federal Institute for NBC-Protection, available at: http://www.labor-spiez.ch/en/akt/pdf/Spiez_Convergence_2014_web.pdf, at page 38.

- the possible use of CRISPR gene drives against wild populations and ecosystems, for example plants or livestock, by actors intent on doing harm;
- use of gene editing techniques to change the characteristics of an infectious disease so that it resists treatment or controls that prevent it from spreading.[492]

7.24 Specifically, the inter-academy meeting report draws attention to the characteristic absence of distinctive evidence of editing having taken place that may make natural and deliberate events, such as disease outbreaks, difficult to distinguish. This is not the case for gene drives, although they present probably the most significant source of concern.[493] Indeed, most respondents to our call for evidence noted that the risks presented by genome editing were not new in kind except, perhaps, in the case of CRISPR-Cas9-enabled gene drive systems although, for the time being, these would probably require the resources of a nation state to deploy offensively.[494] The UK research councils, accordingly, recognise the possibility for misuse of research but express confidence in robust governance procedures for the research that they support and the applicability of existing regulatory frameworks. They advocate a system "based primarily upon self-governance by the scientific community, but drawing on the inputs of other key stakeholders" as the most effective means of managing risks of misuse.[495]

7.25 The viewpoint of the US is somewhat different. It is perhaps a measure of the concern about the unmatched pace of development and diffusion of genome editing – unmatched by parallel developments in governance, policy and culture – that, in February 2016, the US Director of National Intelligence identified genome editing as one of six 'weapons of mass destruction and proliferation' in his report on current global threats.[496] Following this DARPA's Biological Technologies Office is also sponsoring a 'Proposers Day' in advance of a planned Broad Agency Announcement for the Safe Genes Program, initiated in September 2016, with the aim of creating

[492] Response to *Call for Evidence* by the Royal Society.

[493] "Modern genome 'editing' technologies, such as CRISPR/CAS-9 often do not leave 'fingerprints' indicating that that organism has been altered. This conceals attempts to enhance the organism's effectiveness, hampers forensic investigations and complicates the differentiation between unusual and unnatural disease events. Some methodologies do leave 'fingerprints', in particular, the use of a gene drive as the ability to be passed on to the next generation is due to a permanent change to the organism." Inter-academy partnership (2015) *The Biological and Toxin Weapons Convention: implications of advances in science and technology*, available at: https://royalsociety.org/topics-policy/projects/biological-toxin-weapons-convention/, at page 16.

[494] "The skills and resources required remain considerable implying that it would likely require the backing of a nation state, however these barriers are likely to be rapidly eroded over the next few years with new technologies.", response to *Call for Evidence* by the Royal Society. The biosafety and biosecurity "considerations are unlikely to be significantly different in degree or in kind from other R&D using microorganisms, however the consequence of factors such as reduced traceability should be explored." Response to *Call for Evidence* by Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC). "Not different from already existing considerations regarding GMOs. Genome editing is not a new concept that requires genuinely new regulations, it has just become more affordable, and technically attainable than ever before. Thus the risks of misuse, which have always existed when genomes were modified, have now multiplied. There is a strong movement to argue that there is no need for further regulation. However it is unclear if all stakeholders will be content with this position. A qualified discussion about the (long) history of genome editing and what has changed (its affordability and technical achievability) will help to put things into perspective." Anonymous response to *Call for Evidence*.

[495] See response to *Call for Evidence* by Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC). This approach is supported by the joint BBSRC, MRC and Wellcome Trust policy on managing risks of research misuse; see: https://wellcome.ac.uk/funding/managing-grant/managing-risks-research-misuse.

[496] "Research in genome editing conducted by countries with different regulatory or ethical standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products. Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications. Advances in genome editing in 2015 have compelled groups of high-profile US and European biologists to question unregulated editing of the human germline (cells that are relevant for reproduction), which might create inheritable genetic changes. Nevertheless, researchers will probably continue to encounter challenges to achieve the desired outcome of their genome modifications, in part because of the technical limitations that are inherent in available genome editing systems." *Worldwide threat assessment of the US intelligence community* (2016), available at: https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf, at page 9.

biological capabilities that enable the safe pursuit of advanced genome editing applications and derivative technologies such as gene drives.[497]

7.26 In addition to the offensive possibilities suggested above, a number of more speculative concerns have been suggested, among them that genome editing might lead to the development of 'smart' biological pathogens that could affect particular sub-populations selectively or which might be closely controlled.[498] The application of genome editing to enhance the characteristics or performance of combat personnel, what DARPA refers to as 'warfighters', has also been suggested. Concerns expressed here are that the exceptional nature of the martial context might excuse or require exceptional measures, which in any other context would be seen as unacceptable.[499] As with elite sportswomen and sportsmen, military personnel may therefore be in a position of vulnerability as potential research subjects or put under pressure as employees.[500] A further possibility is that genetic modification might make it possible to hide messages in biological tissue, allowing people, animals, plants or microorganisms, or products derived from them, to transmit encoded messages across international borders without detection, raising novel challenges for intelligence and security.[501]

Moral and societal questions identified

7.27 A persistent conceptual question is that of how we should think about or frame the practice of genome editing and its products. On one level this might look, at present, like a domestic question of disciplinary taxonomy for universities and research institutes, except that genome editing shows the potential to disrupt disciplinary formations and their associated forms of organisation, administration and governance. The emergence of synthetic biology suggests how this may happen within the life sciences, although the uses of genome editing exceed the field that synthetic biology has marked out. Thinking about genome editing from the point of view of an established disciplinary knowledge culture may be less appropriate, therefore, than thinking about it in relation to the (expanding number of) contexts and conditions in which it is used. This leads to at least two problematic practical consequences.

7.28 The first relates to how the products of genome editing are taken up into existing governance and regulatory frameworks. The question of whether the product of genome editing is a GMO for the purposes of regulation is not inconsequential – it may determine, for example, the applicability of the Cartagena Protocol and its associated procedures – but it is only the most obvious manifestation of the more profound question of the moral and social significance of the genome editing procedure itself, of the different kinds of interventions that it may enable, and the possible outcomes that are perceived to associate with them. (A similar issue was noted in relation to food and agriculture in section 5.) On the supply side there are potentially very few controls: in interview, a representative of a company supplying genome editing products and services suggested that no procedure existed for verifying the *bona fides* of those to whom they provided products or services (e.g. modified animals, CRISPR editing kits) and that to do so would not be

[497] This programme was announced shortly before initial publication of this report and little information was publicly available at that time; see: http://www.darpa.mil/news-events/2016-09-07.

[498] "The ability to design and edit a pathogen also raises the possibility of attempting to identify genomic targets (and design specific countermeasures) or to design-in time-limited effects or other means to neutralise a biological agent (i.e. means which might make the weapon appear more controllable and make its use more imaginable).", response to *Call for Evidence* by David Albert Jones.

[499] Agamben G (2005) *State of exception* (translated by Attell K) (Chicago: University of Chicago Press).

[500] 'Gene doping' has been on the list of banned doping practices of the World Anti-Doping Agency (WADA) since 2003, although no evidence of its use has yet emerged. See also Wired (28 July 2016) *Olympic drug cops will scan for genetically modified athletes*, available at: https://www.wired.com/2016/07/olympic-drug-cops-will-scan-genetically-modified-athletes/; response to *Call for Evidence* by Angel Petropanagos and Carlos Mariscal.

[501] Response to *Call for Evidence* by Angel Petropanagos and Carlos Mariscal. DNA is an efficient store of information: in 2012 George Church announced that he had encoded his 2012 book *Regenesis: how synthetic biology will reinvent nature and ourselves* in DNA (co-written with Ed Regis) in DNA; the book was approximately 53,000 words (about the length of this report) including images, and Church and his collaborators produced about 70 billion copies of it in the process (considerably more than the print run of this report). See Church GM, Gao Y and Kosuri S (2012) Next-generation digital information storage in DNA *Science* **337**(6102): 1628. See also: Extance A (2016) How DNA could store all the world's data *Nature* **537**(7618): 22-4.

usual, given that the products were approved by the appropriate regulator (in this case the FDA).[502] Genome editing appears to have made distinctions more difficult, both to draw and to enforce, between 'safe' and 'unsafe' in relation either to the technologies or to their users.

7.29 The second practical problem relates to the circumscription of a 'community' of users or practitioners as correspondents in a notional system of moral injunctions and responsibilities, and subject to professional or institutional control and sanction. Whereas the cultural response of the elite 'scientific community' is typically enjoined by a sense of common responsibility, this notion of community may be becoming increasingly attenuated. Beyond the class of elite academic research scientists there is a growing class of scientific professionals and technicians, and, beyond these, a demi-monde of scientifically literate but not scientifically socialised ('disciplined') amateurs and dilettantes, with a variety of interests in genome editing, not all of which may be defined by the pursuit of knowledge 'for the relief of man's estate'.[503] Significantly, in the present case, the very accessibility of genome editing itself may have the potential to undermine the coherence of the community by extending the opportunities of inquiry and technology to those to whom they were previously inaccessible behind barriers of recondite knowledge, unaffordable resource requirements, or membership of a group with strict and technologically meaningful rites of passage. While it may be the case that self-regulation is sufficient for risks that still require the resources of a nation state to realise, this may not continue always to be the case. It might be appropriate to question not what the scientific community can do to recuperate genome editing for itself but what implications the flourishing of accessible techniques in the life sciences might have for the integrity of the hitherto existing scientific community and its power to self-regulate. While the response to this, of the sort that synthetic biologists have self-consciously explored, may lie in the formation of novel sorts of reflective, socially engaged and self-regulating communities (which overrun distinctions between knowledge formations while simultaneously reviving exuberant experimentalism) it is doubtful that it can rely on *discipline* in the conventional academic sense, which requires a defined community of practitioners.[504]

7.30 The overflowing of life science into non-elite discourse and practice, and the speed and promiscuity with which research tools are deployed, characteristic of synthetic biology, has been celebrated by enthusiasts as a 'democratisation' of science. The scale (or scalability) of the technologies probably makes a significant difference here, with biology arguably moving from 'big science' like the Human Genome Project to a handheld scale, at the same time harnessing the accessible design facilities of digital computing in place of wet bench experimentation.[505] It is also facilitated by social developments such as the broadening of access to higher education and to academic conferences, and the spread of information via the internet (and the 'dark web'), and cultural movements within science, such as 'open' publishing and 'open data'. Another factor is the intervention of Silicon Valley-style market capitalism (with crowdfunding flowing into the spaces not taken by venture capitalists) in the innovation system.[506] This raises the question of whether such developments might encourage what economists would call 'market failure' (inefficient allocation of resources) and the production of 'negative externalities' (social costs and harms) that, many would argue, require some form of public regulation. If failures of this kind can be identified or foreseen, and regulation is the correct response, this leads to questions about

[502] Research interview with Ruby Yanru Chen-Tsai, Applied Stem Cell, Inc.

[503] See section 3. Even within the academy, as our work on *Research Culture* shows, the cultural gap between tenured professors and the ranks of postdocs is not diminishing. Concerns about the impact of workload, competition and career structures on early career researchers were reported as factors felt most to threaten the quality and integrity of science.

[504] "High levels of awareness, and appropriate and robust behavioural norms in the science community are vital to ensure that knowledge and wisdom in its humanitarian use develop together. Training and professional standards will be important and particular attention to the sharing of information and resources." Response to *Call for Evidence* by the Royal Society of Biology.

[505] For scale of DNA analysis see Check Hayden E (2015) Pint-sized DNA sequencer impresses first users *Nature* **521**(7550): 15-6.

[506] The ODIN, for example, which makes 140 US dollar CRISPR kits, was set up with crowdfunding in December 2015 – the majority of the 290 backers put in a level of funding equivalent to the cost of the kit (see: https://www.indiegogo.com/projects/diy-crispr-kits-learn-modern-science-by-doing#/).

what kind of regulatory governance mechanisms can be put in place, and have meaningful traction, given potential for the wide variation and geographical dispersal, at times, into relatively uncontrolled environments.

7.31 A related concern is the potential 'democratic deficit' with regard to both the social orientation of research and innovation, and the equitable distribution of benefits. This raises, once again, profound but persistent questions about the preference for, or acceptance of, contingent structural features of innovation systems (like relationship of public and private sector actors involved), which are particularly pertinent at a time when such systems are confronting technological change that is both rapid and of significant potential impact.[507] On one view, the power of research and innovation profoundly to affect the conditions of common existence, and the equitable distribution of costs and benefits, entails a responsibility to society that cannot be divined through market signals, which are too ambiguous, too unequal and too late.[508] Such objections run up against the view that there must be proper limits to intrusion to protect the freedom of inquiry which is necessary for science to refresh itself and develop, and to avoid repeating the historically poor performance of *dirigiste* policies and regimes, as well as the possibility that, however flawed, market signals may be the most workable solution in the circumstances.[509] Whatever the optimum form of governance, the major consideration for this report has been the speed of development and diffusion of the techniques of genome editing relative to the social processes by which normative frameworks, such as those of law, regulation and public acceptance evolve. The possibility of attenuation or fracture of this relationship between the scientific and normative knowledge warrants further examination.[510]

Conclusion

7.32 As in most areas that we have considered, the major impact of genome editing derives from the broad applicability, speed, efficacy and accessibility of the techniques. In industrial applications genome editing promises to further the existing aims of conventional genetic engineering and synthetic biology. It is complicated, however, by the fact that the accessible features of genome editing may themselves exacerbate the transformation of research from a relatively elite activity, removed to academic institutions and industrial corporations, to something that is open, diffused and integrated with technology and markets. This is compounded by the speed of development, which potentially places stress on the relationship between scientific knowledge and technical capacities, and the normative frameworks within which they are applied.

7.33 A distinct set of issues concerns research that has potential military or terrorist applications. Although genome editing does not generally raise issues that are different in kind from previous research, the fact that genome editing makes the implementation of this research easier is a matter for serious consideration (for example, in relation to the Biological and Toxin Weapons Convention). New possibilities raised by convergence of genome editing and gene drive technologies may become a matter of increasing concern as the technologies develop. There are also other issues in a military context that require monitoring, such as the vulnerability of military personnel as potential research subjects and the question of legitimate enhancement.

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[507] These issues were also covered in *Emerging Biotechnologies*. The question may be formulated as the dilemma of *dirigisme* or *laissez faire* over which successive governments have vacillated.

[508] "Scientists need to be responsible to society: It may be beneficial for those who wish to pursue a career in this field [gene-editing], especially those who oversee or direct laboratory research to undertake training or a period of sustained advanced-learning that goes 'beyond ELSI' [Economic, Legal and Social Issues] to cover 'PEELSA-ST' (political, economic, ethical, legal and social aspects of science and technology) (see Calvert et al. 2015). Scientists themselves must be enabled through reflexive tools and social theory to critically assess the ways in which their work or innovation meets the needs of society, and reflect upon who defines those needs and why and whose needs are or are not considered? This will allow researchers to better engage and deliberate with ethicists, social scientists, stakeholders, various publics and policy makers about the socially desirable orientation of research and innovation," anonymous response to *Call for Evidence*. See also: Balmer A, Calvert J, Marris C, *et al*. (2015) Taking roles in interdisciplinary collaborations: reflections on working in post-ELSI spaces in the UK synthetic biology community *Science and Technology Studies* **28** (3): 3-25.

[509] "It is in turn important that scientists be allowed the contained spaces to pursue basic research unhindered (to the extent possible) by overriding concerns for public acceptance or commercialization. Scientists should also be allowed to carry out fundamental research without fear for their personal safety", anonymous response to *Call for Evidence*.

[510] See section 2 above.

Section 8

Conclusions

Section 8 – Conclusions

Outline

The difficulty of predicting how technological innovations are likely to develop is noted and the approach taken in the report is reviewed.

The features of genome editing, in particular the CRISPR-Cas9 system, that give rise to significant ethical questions are reviewed, including the novelty of the mode of action, accessibility (including low cost and level of knowledge and resourcing required), speed of use from design to results and of uptake across life science sectors, and potential to achieve multiple simultaneous edits.

The role of ethical reflection with regard to different applications of genome editing is proposed: three sorts of inquiry are recommended.

Societal and moral issues identified in the report for further consideration are divided into those that should be addressed urgently, those that may fall to be addressed in the near future and those that should be kept under review.

8.1 This review has confirmed the impression of rapid uptake and diffusion of genome editing across many fields of biological research. This spread is overwhelmingly attributable to the CRISPR-Cas9 system, although that technique is itself still undergoing refinement. Indeed, new technologies may emerge that could affect genome editing with even greater precision and speed. There are, nevertheless, variations in the purpose and pattern of use between different fields of research. Although the impact of genome editing in research is already impressive many of the issues we have identified anticipate the potential future uses of genome editing as a core component of many new treatments and technologies. Predicting the future of technological developments is notoriously difficult. At a gross level, a number of common tropes warn of the potential errors of both over-expecting and under-anticipating the impact of new technologies.[511] This difficulty applies not only to the timescale according to which productive applications emerge, but also the directions that technological development may take. It should be remembered that most prospective technologies fail, and that some lead to undesirable consequences, a fact often obscured by 'whig' histories that reconstruct the history of successful technologies and their beneficial social consequences. Scientific discovery and technological innovation is important but not inevitable. Most important among the factors shaping technological development is human agency. It is human agency, in terms of decisions that are made about directions of research, funding and investment, the setting of legal limits and regulatory principles, the design of institutions and programmes, and the desire for or acceptance of different possible states of affairs, that will determine whether, and which, prospective technologies emerge and, ultimately, their historical significance.

8.2 In this review our approach has been analytic: we have looked into the technology of genome editing, isolated aspects of it and examined the part it may play in different settings. From the beginning, however, we have anticipated a second phase of our work, in which we will develop normative conclusions, advice and recommendations. The starting point for this work will not be the technology itself but rather one or more fields of activity, 'challenges' or 'problems' in which genome editing emerges and on which it is having or is expected to have an impact.

[511] The so-called 'First law of technology', usually attributed to US scientist and futurologist Roy Amara, states that the impact of technology tends to be overestimated in the short term and underestimated in the long term. The Gartner consultancy's widely-cited 'hype curve' suggests that initial over-excitement about technology usually leads to disillusionment followed by gradual productivity gains. These have in common with the 'productivity paradox' (famously noted by the economist Robert Solow with reference to electronic computing technology) the suggestion that delayed productivity may be less about the intrinsic features of the technology than about its embedding within, and transformation of, systems of production and associated conditions. In *The shock of the old*, the historian of technology David Edgerton warns against neophilia distorting judgements about the overall social importance of different technologies. See: Edgerton D (2008) *The shock of the old: technology and global history since 1900* (London: Profile Books).

What is ethically challenging about genome editing?

8.3 A number of features of genome editing, especially CRISPR-Cas9 and analogues, have emerged from our inquiry as sources of issues that require further ethical consideration:

- **Novel mode of action.** In a research context genome editing is demonstrably effective at making small, precise and specific edits to DNA in living cells. This means that it can be used to 'knock out' genes or to change their function by adding or replacing sections of DNA. It is a significant feature of the CRISPR-Cas9 technique that these 'edits' need not leave any tell-tale trace of their origin in the genome, in the sense that subsequent genome analysis is able to tell whether they have been introduced intentionally or arisen through common or garden random mutation. Variations of the technique, currently being developed, could achieve similar effects at the epigenomic level. These features challenge distinctions (like that between GMOs and non-GMOs) on which important aspects of normative systems, like the system of food regulation in the EU, are based. The ambiguity produced by genome editing challenges us to think about what is significant about such distinctions and to review our moral attitudes and practical measures accordingly.[512] Similarly, the theoretical possibility of changing a disease-causing point mutation in the genome of an early human embryo into a common, non-disease causing variant, without any other alteration, challenges us to reconsider the reasons for existing prohibitions on deliberately causing genomic alterations that may be inherited by future generations. Finally, the significance of epigenome alterations as opposed to genome alterations, or alterations of other kinds in biological systems, and how these fit with existing norms, would benefit from greater attention in the context of what CRISPR-Cas9 might achieve.

- **Accessibility.** Compared to previous techniques for genetic manipulation, and to previous editing systems, CRISPR-Cas9 and its analogues are comparatively affordable and easy to use. The fall in cost of genome manipulation can be compared to that of semiconductor technologies and genome sequencing. But it is especially as a technology *converging with* semiconductor and genome sequencing technologies, and other technologies that are also rapidly descending in cost and increasing in power, that genome editing holds genuinely transformative potential. The incorporation of genome editing into proprietary technologies and kits that are both affordable and approachable by a greater number of users, including users outside élite communities and institutional settings, challenges us to think about how ethical reflection and governance systems can engage effectively with technology use (if not through élite communities, institutions, learned and professional bodies, traditional businesses, etc.). Similarly, the range of interests potentially engaged by the directions in which genome editing technologies may develop represents a challenge to the principles of scientific and commercial freedom, and to political procedures for discovering and asserting the public interest (including the protection of potentially disadvantaged groups).

- **Speed of use and uptake.** Closely related to the cost and ease of use, the increased speed with which genome editing allows genetic manipulation to be achieved (within the context of a research project, for example) and the speed of its uptake and diffusion among use contexts may exacerbate uncertainties or ambiguities that exist in applying governance systems and existing norms. This speed and diffusion makes what might have been a difficult but limited and local problem into a widespread and highly consequential one. In many cases (as with the governance of medical and reproductive innovations in the UK) there may be existing provisions that are be both applicable and robust. They may not, however, be optimal (for example, given the novelty of the mode of action discussed above). Optimising them is important because there are ethical considerations on both sides (for example, in favour of both liberalising and of constraining the use of the technology; it is not simply that technology

[512] While these distinctions may *appear to be questions of fact susceptible of straightforward answers, we hold that the answers to such questions in fact are complex amalgams of factual and moral judgements* or the result of political compromise. (The italicised words are taken from the Report of the Committee of Inquiry into Human Reproduction & Embryology (the 'Warnock Report') 1984 (Cmnd 9314) (London: HMSO).

moves inexorably in one direction and ethics restrains it). Speed of innovation may perturb the balance between these considerations. Differences in the speed of development of research and innovation compared to the pace of development of related systems, including normative systems (for example, changes to the law, to institutional structures, regulatory policies and procedures, and the evolution of public moral consensus) can, likewise, exacerbate conceptual inconsistencies, increase anxiety and give rise to distrust. Such differences call for new terms of reconciliation between biomedicine and biotechnology and society. In an open society the establishment of these terms requires effective social processes, which may be hampered by restrictions on the flow of information, or the inconsistent assignment of social meaning.[513] A further source of concern is that speed of diffusion may cause technology to become prematurely locked in, before the implications have been explored and evaluated adequately, or before related systems needed to optimise it are able to catch up.[514] (We heard in evidence how it is difficult to get papers published and obtain grants in certain fields without genome editing as part of the methodology; this suggests a potential, at least, for genome editing to crowd out other research, or change the deployment of research resources such as laboratories and staff, or even change the aims of research to those that are more amenable to genome editing.)

- **Multiplexing.** A final reason for further ethical reflection on genome editing is the potential to achieve multiple edits in a given genome. This could revive the prospects of techniques such as xenotransplantation, by overcoming limitations that have constrained them in the past. Although xenotransplantation has been discussed at length, genome editing may constitute a significant change in the context of these debates.[515] Multiple, simultaneous (multiplex) editing, or multiple rounds of editing in successive cell lines (followed by nuclear transfer cloning techniques or direct reprogramming of cells to gametes), could, additively, achieve large-scale genetic alterations, potentially creating synthetic genes or transgene analogues, or developing complex synthetic organisms or organic components. In this respect it is a potentially significant enabler of future synthetic biology and a potential disruptor of established species classifications.

What role should ethical reflection play?

8.4 The focus on the technology tends to obscure rather than reveal the social and ethical issues. It also masks questions that arise at different spatio-temporal scales.[516] (Earlier, we noted the potentially misleading use of 'precision' when talking about genome editing, given that the functional outcomes at the level of the organism in its environment are not precisely prescribed, or may be so only in exceptional cases). Advances in knowledge about which target sequences have a predictable phenotypic effect when altered and methods of delivering the genome editing machinery into living cells at high efficiency are, potentially, at least as significant as the discovery

[513] Popper K (1945) *The open society and its enemies* (London: Routledge).

[514] "By the end of 2014, CRISPR had been mentioned in more than 600 research publications. [This figure has, as of June 2016, more than doubled.] "[…] 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.

[515] Xenotransplantation was discussed extensively in the final decade of the last century (e.g. Nuffield Council on Bioethics (1996) *Animal-to-human transplants: the ethics of xenotransplantation*, available at: http://nuffieldbioethics.org/project/xenotransplantation/). In 1997, a regulatory authority, the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA), was established in anticipation of imminent medical treatments. But the technique foundered on a number of technical hurdles. UKXIRA was disbanded in 2006. See: McLean S and Williamson L (2007) The demise of UKXIRA and the regulation of solid-organ xenotransplantation in the UK *Journal of Medical Ethics* **33**(7): 373-5.

[516] Some of the discussion of genome editing implies or, at least, does nothing to counteract the impression of lingering genetic determinism: the belief that genotype strongly determines phenotype. This impression may be partly a hermeneutic phenomenon: a consequence of inattention to context, for example taking scientific papers out of their implicit frame of reference. But this does not diminish the importance of careful communication and translation of ideas between audiences and discourses.

of effective genome editing techniques and will not necessarily be deliverable in every desired case (or, indeed, in most, or even in many cases).

8.5 We are convinced that it makes little sense to treat the questions raised by genome editing as if they belonged to a single field (a hypothetical discipline of 'genome editing studies').[517] Rather, they should be addressed as part of different technology convergences (e.g. with ART, with gene drives, with agricultural technologies, etc.), which also includes political technologies (regulation, legislation, etc.). But, more than that, we conclude that it is not the scale at which questions are posed but also their orientation that is important. Beginning with questions about what can be achieved at the genome level risks reducing all questions to 'ELSI' questions (questions about the ethical, legal and social implications of genome editing, as if that were the only or most obvious pathway available to address a complex set of real world challenges) and leaving questions about the appropriateness of genome technologies in any given case unaddressed. This is why the next, normative, phase of our work should begin with problems or challenges (and the potential diverse framings of those challenges), rather than technologies, and adopt a comparative methodology.

8.6 In the light of the inquiry to date, we conclude and recommend that this second stage of work should involve at least three elements:

- an account of the value commitments that are at stake in the distinctions that are made in existing governance arrangements that are effective in the area under consideration (and in any proposals to revise these);
- an identification of where public and private interests are mutually engaged, and the legitimate force of these (i.e. who is entitled to determine what may or should be done?);
- a comparison of the different visions of desirable future states of affairs and narratives about technological and social developments, which continually re-imagine possible outcomes, feeding back into a public discourse informing governance.

Triage of issues for ethical consideration

8.7 We divide the issues that we have identified in our inquiry to date into three categories: those that should be addressed urgently, those that may need to be addressed in the near future, and those that should be kept under review. Because, as we have argued, the questions should be situated within a particular sociotechnological context (a historically and geographically defined site where social and technological conditions interact) the questions are elaborated below in relation to prospective uses of genome editing and that, therefore, define a proposed programme of further work.

Issues that should be addressed urgently

Human reproduction

8.8 Of all the potential applications of genome editing that have been discussed, the one that has consistently generated most controversy is the genetic alteration of human embryos *in vitro* and the possibility that altered embryos could be transferred to a woman who would give birth to a human being with a unique, altered genome. In identifying this as a question that should be urgently addressed we do not mean to imply that such a birth is imminent.[518] The safety and efficacy of the genome editing technique has not been demonstrated sufficiently through research in human embryos and, in the UK at least, it would be a criminal offence to transfer an edited

[517] The analogy to nanotechnologies, suggested by a respondent to our *Call for Evidence*, is apt here: see response by Donald Bruce.

[518] Controversialists have, nevertheless, predicted that such a child will be born somewhere in the world within the next couple of years or has already been born.

embryo to a woman unless the law were to change to make it permissible, a process that would undoubtedly take a number of years, even if the wheels were to be set in motion without delay.

8.9 The reasons for considering this urgently are therefore not because the applications are imminent, but because the path, if it is to be embarked upon, will be a long one, and will be made longer if departure is delayed. Deciding whether it should be broached *at all* is therefore both pressing and ethically highly complex, and therefore likely to be difficult to resolve. But if the conclusion of this process is that applications of this sort should be permitted, it is better that they should be available as soon as possible. (The moral arguments in favour include the alleviation of human suffering and prolonging implementation would, all other things being equal, extend this suffering.)[519] It is also preferable for ethical reflection to shape the course taken rather than to appear as a final hurdle to 'overcome' when the research has already been accomplished, resources committed, and hopes and fears piqued. Such reflection can also help to mitigate the risk of path dependency and ensure that alternative avenues of research continue to be considered. Addressing this issue now will help to meet concerns that research and technology development is rushing ahead of public debate and allow such debate to influence the development of the technology, distinguish acceptable from unacceptable aims, and reduce the uncertainty and ambiguity under which researchers and potential beneficiaries live. Furthermore, the strength and unreconciled diversity of public opinion in this area cannot be denied and constitute, in themselves, good reasons for engaging with it.

8.10 Research undoubtedly has a very long way to go before any application of this sort could be contemplated. But whereas therapeutic applications of genome editing to address existing disease states face challenges in terms of delivery and achieving efficiency *in vivo*, altering a point mutation (or a small deletion) in a human embryo without harming the embryo's development is potentially a closer prospect based on research in model organisms. We already stand to learn much about the use of genome editing in human embryos from research that has recently been approved by the HFEA.[520] The principal challenges in this case are the very difficult questions of what would be required to demonstrate safety and efficacy, and resolving the ethical arguments for and against attempting it.[521] It is, furthermore, an issue that the Council is well placed to take up, following from the observation at the end of our 2012 report *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* that:

> "the wider policy debate could benefit from a fuller discussion of the ethics of different kinds of prospective and theoretical germline therapies. This would include potential therapies that would act on the cell nucleus with heritable effects, and therapies which might involve nuclear transfer in its various forms. The ethical robustness and sustainability of policy decisions made around cell reconstructive therapies and other potential treatments for serious genetic disorders would benefit from a thorough discussion of the full range of these other prospective treatments."[522]

8.11 Despite the amount of consideration that these questions have received the controversy remains unresolved. We do not believe, however, that this is the result of an intractable opposition of principled positions, but of complex judgments made in a changing context of relevant factors. Many features of this context have changed since current policy positions were established, even since 2012, the development of genome editing technologies not the least of them.

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[519] In this respect the arguments are analogous to successful arguments for permitting research on human embryos that would lead to the development of stem cell therapies – the sooner the research is achieved, the sooner the therapies might be available, and affected people could be treated.

[520] See http://www.hfea.gov.uk/10187.html.

[521] Although raising distinct issues in many respects, relevant consideration of what is required to demonstrate sufficient levels of safety and efficacy for translation into clinical use is currently being undertaken in the UK in relation to cell reconstruction techniques for the avoidance of mitochondrial disorders (so-called mitochondrial donation).

[522] Nuffield Council on Bioethics (2012) *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*, available at: http://nuffieldbioethics.org/project/mitochondrial-dna-disorders/.

Livestock

8.12 Genome editing offers a potential set of responses to the challenge of developing and maintaining a sufficient supply of safe, nutritious food. As we observed in the section on food, research on the genetic alteration of livestock is comparatively well advanced, and some of the threats to current systems of husbandry (such as livestock diseases) that it may be used to address are well understood. These two factors make this a significant topic. There is, furthermore, considerable difference of moral opinion about the appropriate role of different foods and husbandry methods in relation to the overall challenge of food security. At the most general level, there are debates about the relative contributions of animal and vegetable resources to the food supply. All these debates are potentially affected and possibly exacerbated by changes in the relative efficiencies of different food production methods that might be brought about by genome editing.

8.13 Given its imminence, and in contrast to the very considerable public debate that has surrounded genetically modified crops, comparatively little attention has been given to genetic livestock manipulation and its regulation (at least where the animals concerned may not be regarded as 'genetically modified organisms' as defined in relevant legal instruments). Much attention has, however, been given to alternative methods of husbandry and the role of livestock of different kinds in meeting people's needs and desires for food. Genome editing may play a potentially significant, though morally ambiguous, role in relation to sustainability, intensity, yield, human and animal welfare and quality.

8.14 Particularly strong feelings are aroused by issues surrounding animal welfare. It is possible, though certainly not obvious, that genome editing could have direct effects on animal welfare. More likely, it could have indirect effects by making feasible different regimes for raising animals. Cattle genomically modified to lack horns, for instance, might potentially be kept in denser populations than would otherwise be possible. A reasonable debate on these issues is likely to be fostered by careful attention to as wide as possible a range of ways in which genome editing might affect animal welfare.

8.15 As with human applications, questions arise about the appropriateness of existing regulatory distinctions and the complex reasons, some of them ethical reasons, that underlie them. It is appropriate to ask, therefore, whether there is a need for new classifications or new approaches to policy and regulation. Also, as in the case of human applications, questions arise about the nature and force of the public interest, how this may affect commercial freedoms and welfare considerations, and what the appropriate scope and modalities of regulation should be. The answers to these questions will have important consequences for businesses, international trade, and the economics of food production.

Questions that may need to be addressed in the near future

Editing of wild animal species to prevent disease transmission

8.16 The use of gene drive technology has already been noted as raising significant public ethical issues and has been the subject of inquiries by major national bodies.[523] The combination of gene drives with genome editing technology potentially raises additional issues by enabling previously intractable obstacles to be overcome and therefore, a greater number of aims to be pursued. The most significant of these, currently, is the alteration of mosquitoes to prevent the transmission of tropical diseases. There are very significant concerns about the ecological risks of releasing gene

[523] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and; House of Lords Science and Technology Select Committee in its report *Genetically modified insects* (2015), available at: http://www.publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/68.pdf.

drives into wild populations although the likelihood of these risks materialising is a matter of scientific disagreement.

8.17 There are, however, established international regulatory pathways for release of GM mosquitoes, which mean that environmental release would have to take place in a controlled and staged manner, through successive trials, which entail a significant cost burden for developers. Key considerations must be robustness, reversibility and control: whether an intervention is able to retain structure and efficacy while adapting readily to major environmental change and/or other major challenges, whether it is reversible and whether it is local or systemic. From the current stage of development of genome editing-enabled gene drives, large-scale release is likely to be at least a decade away. However, this does not mean that ethical examination is currently not required. There is much work to do to ensure that, at the very least, development of the technologies in any geographical area takes proper account of the values, priorities and preferences of the communities affected.

Xenotransplantation and humanised animals

8.18 As noted above, the potential capacity of genome editing to overcome bottlenecks in xenotransplantation research, for example, in terms of reducing the risk of zoonosis (the transmission of viruses between animals and humans), or in terms of addressing adverse immune response suggests that new routes to treatment of diseases requiring tissue or solid organ transplants may open up. Many of the ethical questions regarding xenotransplantation have been debated in the past although, as research progresses, these may need to be recalled for a new generation and the question of appropriate regulation may need to be revisited.

Questions that should be kept under review

Cell-based therapies

8.19 One of the most promising areas of development using genome editing is cell based therapies for existing diseases (discussed in section 4). These raise a number of difficult questions with regard to demonstrating safety and utility, and about when they should be introduced into clinical practice and applied to particular patients. We do not feel, however, that for the most part the issues raised are distinctively different for genome editing.

8.20 There exist clinical trials and approvals protocols for pharmaceuticals and medical devices that provide for these questions to be addressed. Partly because of these, therapies currently under development are likely to take some time yet to get into clinical practice. We have noted the tension between following these protocols and the imperative to get effective treatments to patients in serious need. And there has been some concern among researchers about the confusion between genome editing research on somatic cells and research on embryos. However, these do not appear to have a peculiar force in relation to genome editing or be incapable of being addressed in existing ways.

Plant science

8.21 We noted that genome editing is unlikely to have the same transformative impact in plant breeding as in other areas of biomedicine and biotechnology, at least without significant advances in other areas of knowledge and technical capability needed to produce predictable and stable phenotypes from genetically altered plants. It is likely that many new plant varieties produced with the use of genome editing may not be regarded as genetically modified organisms (GMOs). Others may, however, be regarded as GMOs. How that distinction is drawn will be potentially significant, given the regulatory burden that the GMO classification places on producers. This classification is, in any case, likely to be the site of a boundary dispute between biotechnology companies and civil society organisations with principled reservations about the use of genome technologies in food production. It may also have a significant effect on shaping the industry, including the new non-GMO biotechnology space, which might provide an entry point for a new wave of small and medium sized enterprises. It will be important that this is kept under review since it may have

implications for the direction or speed of development of a new generation of plant varieties with beneficial characteristics such as drought tolerance or increased nutritional benefits (see section 5).

Changing patterns of technology use

8.22 A larger and more amorphous set of questions arises from our consideration of genome editing outside the relatively well-defined spaces of biomedicine, agricultural biotechnology and public health. We noted that genome editing constitutes an important enabling technology for synthetic biology, and therefore for industrial biotechnology, and may have potentially beneficial applications in, for example, the production of high-value chemicals, materials and biofuels. (Whether they are publicly beneficial or not may depend largely on the economic conditions under which they are developed and introduced.)

8.23 While the private biotechnology sector is defined, if somewhat opaque, we noted that there are a number of even more opaque, less well-defined, or interstitial sites, outside the more-or-less transparently and more-or-less well governed spaces of recognised institutions, communities of experts and commercial firms. These include military and national security initiatives, artistic and cultural activities, and private experiments by community groups or individuals. Many of these are enabled by the accessibility of genome editing, noted above, and prompt questions about who 'owns' technology and their relationship with normative systems, if this is not through traditional professional or learned bodies, institutions, or communities. It suggests a need to consider the implications of an uncontrolled diffusion of powerful genome technologies, especially outside institutional settings. But it also indicates that applying normative systems only to traditional hierarchical social structures will increasingly overlook significant numbers of relevant actors and that new ways of engaging users of technology in moral communities may need to be found.

8.24 The likelihood of someone outside a well-resourced institutional or commercial setting accidentally (or deliberately, if they are a hostile non-state actor) generating a biohazard that presents a serious threat to themselves or the public may be remote currently, although this should be kept under careful review. It is welcome, in this context, that the scientific community and the national security agencies have, from their separate perspectives, responded prospectively to these possibilities.

Appendices

Appendix 1: Method of working

Background

The Nuffield Council on Bioethics commissioned a background paper on genome editing[524] in late 2014, and held a scoping workshop on ethical and regulatory challenges in genome editing in April 2015. The Working Group on Genome Editing was established in September 2015.The Working Group met five times over a period of 10 months. In March 2016, Sciencewise and the Nuffield Council on Bioethics also co-hosted a workshop on genome editing and public dialogue.[525]

In addition to research undertaken in-house, correspondence and engagement with other policy bodies, the Working Group held an open call for evidence, and a series of fact-finding meetings and research interviews with external stakeholders and invited experts to further inform its deliberations. It also received comments on a draft of the Report from six external reviewers. Further details of each of these aspects of the working group's work are given below and in Appendix 2. The Working Group would like to express its gratitude to all those involved for the valuable contribution they made to the project.

Call for evidence document

The Working Group launched a call for evidence in November 2015, which ran until February 2016. Fifty-four responses were received, of which 15 were submitted by individuals and 39 on behalf of organisations. A full list of those responding is set out in Appendix 2. Copies of individual responses will be made available on the website in those instances where the Council has permission from respondents to do so.

Fact finding

As part of its work, the Working Group held a series of fact-finding meetings, the details of which can be found below. Affiliations were correct at the time of the meetings.

Perspectives on genome technologies: 11 November 2015

- Professor Donna Dickenson, Emeritus Professor of Medical Ethics and Humanities, University of London; fellow, Ethox and HeLEX Centres at the University of Oxford; visiting fellow at the Centre for Ethics in Medicine, University of Bristol
- Dr Stephen John, Lecturer in the Philosophy of Public Health, Department of History and Philosophy of Science, University of Cambridge
- Professor Brigitte Nerlich, Professor of Science, Language and Society, University of Nottingham
- Professor Robert Song, Professor in the Department of Theology and Religion, Durham University

Genome editing in plant science: 11 November 2015

- Dr Patrick Middleton, Head of Engagement, BBSRC
- Dr Vladimir Nekrasov, Postdoctoral Scientist, Sophien Kamoun Group, The Sainsbury Laboratory, Norwich
- Dr Thomas Saylor, non-Executive Director, Arecor; Chair of the EuropaBio SME platform

[524] Newson AJ and Wrigley A (2015) *Identifying key developments, issues and questions relating to techniques of genome editing with engineered nucleases*, available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-Editing-Briefing-Paper-Newson-Wrigley.pdf.

[525] The report of this workshop is available at: http://nuffieldbioethics.org/wp-content/uploads/Public-Dialogue-on-Genome-Editing-workshop-report.pdf.

Genome editing and animal research: 25 January 2016

- Dr Luke Alphey, Group Leader, Vector-borne Viral Diseases at The Pirbright Institute
- Professor Charles Godfray, Department of Zoology, University of Oxford
- Dr Sarah Hartley, Research Fellow (science, ethics and public policy), School of Biosciences, University of Nottingham
- Dr Tony Nolan, Senior Research Fellow, Department of Life Sciences, Imperial College London

Biomedical research and applications: 24 February 2016

- Professor Peter Braude, Emeritus Professor, Women's Health, King's College London
- James Lawford Davies, Partner, Hempsons
- Tim Hunt, Senior Vice President of Corporate Affairs and Alexandra Glucksmann, Chief Operating Officer, Editas Medicine
- Dr Robin Lovell-Badge, Group Leader, Francis Crick Institute, London
- Professor Paul Martin, Department of Sociological Studies, University of Sheffield
- Rev Dr Brendan McCarthy, Policy adviser on medical ethics, health and social care policy, Church of England
- Professor Waseem Qasim, Professor of Cell and Gene Therapy, Institute of Child Health, University College London
- Dr Mark Robertson, Director, Global Science Policy, AstraZeneca
- Elizabeth Thomas, Solicitor, Hempsons
- Simon Wright, Partner, Patent Attorney, J A Kemp

Research interviews

In order to explore specific issues and positions in more detail, the Working Group held interviews with the following individuals on a variety of aspects relevant to genome editing research:

- Professor Jackie Leach Scully, Policy Ethics and Life Sciences (PEALS) Centre, Newcastle University
- Dr Marcy Darnovsky and Elliot Hosman, Center for Genetics and Society
- Dr Darren Nesbeth, Department of Biochemical Engineering, University College London
- Regulatory and policy expert, Monsanto
- Professor Jinsong Li, Shanghai Institutes for Biological Sciences (responded in writing)
- Dr Jonathan Lightner, Genus
- Dr Ruby Yanru Chen-Tsai and Maki Ogawa, Applied StemCell, Inc.
- Professor Nicola Spence, Department for Environment, Food & Rural Affairs
- Professor Glyn Hewinson and Professor Trevor Drew, Animal and Plant Health Agency
- Dr Ismail Serageldin, Library of Alexandria

External review

An earlier version of this report was reviewed by six individuals with expertise in disciplines relevant to different aspects of the project. These individuals were:

- Professor Richard Burian
- Dr Sarah Hartley
- Mr Julian Hitchcock
- Dr Darren Nesbeth
- Professor Jackie Leach Scully
- Professor Bruce Whitelaw

The Working Group deeply appreciates the time and thought the reviewers brought to this task and thanks them for their helpful contributions.

The views expressed within this report are those of the Working Group and the Council, and do not necessarily reflect the views of any participants in the various activities undertaken by the Working Group in connection with this report.

Appendix 2: Call for evidence

The aim of the call for evidence was to obtain evidence to inform the Council's examination of ethical issues arising in relation to genome editing research from a wide range of organisations and individuals interested in this area. A background document and guide questions were published online and made available in hard copy on request. Individuals and organisations that the working group expected to have a particular interest were also directly alerted by email and encouraged to respond. The document was divided into six sections:

- Perspectives on genome modification
- Genome editing in plant science
- Genome editing in animals
- Genome editing in microorganisms
- Biomedical research and human applications
- Military and security considerations

In total, 52 guide questions were posed, and respondents were encouraged to answer as many, or as few, as they wished. Fifty-four responses were received, 15 from individuals and 39 from organisations. Three respondents wished to remain anonymous. All the responses were circulated to working group members and a summary of responses was considered in detail at a subsequent working group meeting.

Individual responses will be published in full on the Council's website, where respondents have given permission to do so. The responses received played an important role in shaping the working group's thinking, and the working group is grateful to all those who contributed.

In addition, the working group approached a number of representatives of faith groups for evidence and opinion and received a number of considered and informative responses.

Anonymous

Three respondents wished to remain unlisted.

Individuals

Names, titles and affiliations are given as indicated by respondents unless where adapted for clarity.

- Donald Bruce
- Carolyn Riley Chapman, Ph.D.
- Sarah Hartley, University of Nottingham
- Mr Julian Hitchcock
- Professor David Albert Jones
- Catherine Kendig
- Paul Knoepfler
- Dr Calum MacKellar
- Roshni Namboodiry
- Dr Helen O'Neill PhD
- Dr Nikki Osborne
- Angel Petropanagos, Dalhousie University and Carlos Mariscal, Dalhousie University & University of Nevada, Reno
- Rupert Read, Philosophy Dept., University of East Anglia

Organisations

- Academy of Medical Sciences
- Agricultural Biotechnology Council
- Association of Medical Research Charities

- Association of the British Pharmaceutical Industry
- BioIndustry Association (BIA)
- Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC)
- BrisSynBio, a BBSRC/ EPSRC Synthetic Biology Research Centre
- British Society of Plant Breeders Ltd.
- Center for Genetics and Society
- Christian Action Research & Education (CARE)
- Christian Medical Fellowship
- Comment on Reproductive Ethics (CORE)
- Compassion in World Farming
- Cystic Fibrosis Trust
- EcoNexus
- Friends of the Earth Australia
- GARNet
- Genetic Alliance UK
- GM Freeze
- Greenpeace
- Hindu Council UK
- Mary Lyon Centre, MRC Harwell
- Mission and Public Affairs Council, Church of England
- Muscular Dystrophy UK
- Muslim Council of Britain
- NBT Platform
- Office of the Chief Rabbi
- PHG Foundation
- Progress Educational Trust
- REGenableMED consortium
- Royal Society
- Royal Society of Biology
- Sikh Missionary Society UK
- Target Malaria
- The Sainsbury Laboratory and The John Innes Centre
- Vlaams Instituut voor Biotechnologie (VIB)
- Wellcome Trust
- Xenoislet and TransLink Projects

Appendix 3: The Working Group

Dr Andy Greenfield (Chair)

Council Member and Programme Leader, Mammalian Genetics Unit, Medical Research Council Harwell Institute; HFEA member.

Andy's research focuses on the genetics of sex determination and uses of genome editing. He has been interested in ethics throughout his career.

Professor Richard Ashcroft

Professor of Bioethics in the School of Law, Queen Mary University of London.

Professor Ashcroft is a member of the Tobacco Advisory Group of the Royal College of Physicians and has served as a member of the Gene Therapy Advisory Committee, the ethics committee of the Royal College of Obstetricians and Gynaecologists and the ethics of research and public involvement committee of the Medical Research Council. He is a Fellow of the Royal Society of Biology. He works on the role of human rights theory, law and practice in bioethics policy, and on ethical challenges in public health. He has a longstanding interest in biomedical research ethics.

Professor John Dupré

Professor of the Philosophy of Science, Exeter University and Director, EGENIS, the Centre for the Study of Life Sciences.

Professor Dupré has written on a wide range of topics in the philosophy of biology, including genomics, taxonomy, evolution and human nature. His most recent books are *Genomes and what to make of them* (with the sociologist Barry Barnes) and *Processes of life*. He is a Fellow of the American Association for the Advancement of Science.

Dr David Lawrence

Council Member, Chair of the UK Knowledge Transfer Network and Non-Executive Director at Syngenta AG.

Dr Tony Perry

Dr Tony Perry is Head of the Laboratory of Mammalian Molecular Embryology at the University of Bath. During his work on the establishment of totipotency in mammals he has authored first reports of mouse and pig cloning and of new methods of transgenesis and genome editing. He is interested in developing mammalian genome manipulation and promoting its constructive implementation.

Professor Charis Thompson

Professor of Sociology, London School of Economics and Political Science, and Chancellor's Professor of Gender & Women's Studies and a former Director of the Science, Technology, and Society Center at University of California, Berkeley.

Professor Thompson has written monographs on stem cell research and reproductive technologies and is currently completing a book on science and democracy in the age of technology elites. She serves on several journal editorial boards and committees, including the World Economic Forum's Global Future Council on Technology, Values and Policy.

Professor Christine Watson

Professor of Cell and Cancer Biology in the Department of Pathology, University of Cambridge and the Vice-Principal of Newnham College.

Professor Watson is a mammalian cell biologist and her research is focussed on the developmental biology of the mammary gland and the mechanisms of breast tumourigenesis. She uses CRISPR/Cas9 technology to study the role of individual genes in mammary stem cells and in processes such as cell death and lactation.

Professor Karen Yeung

Professor of Law, King's College London.

Professor Yeung's research interests lie in two broadly defined fields of governance: understanding regulatory governance regimes, and the regulation and governance of, and governance through, new and emerging technologies.

She has written widely on regulation, the central theme of her research being the implications of design-based regulatory techniques for accountability and legitimacy, including the way in which they implicate (or fail to implicate) democratic, constitutional and ethical values. This involves three areas of interest: big data, machine intelligence and predictive analytics, the transnational regulation of technological risk, and the re-design of biological organisms for non-health-related goals.