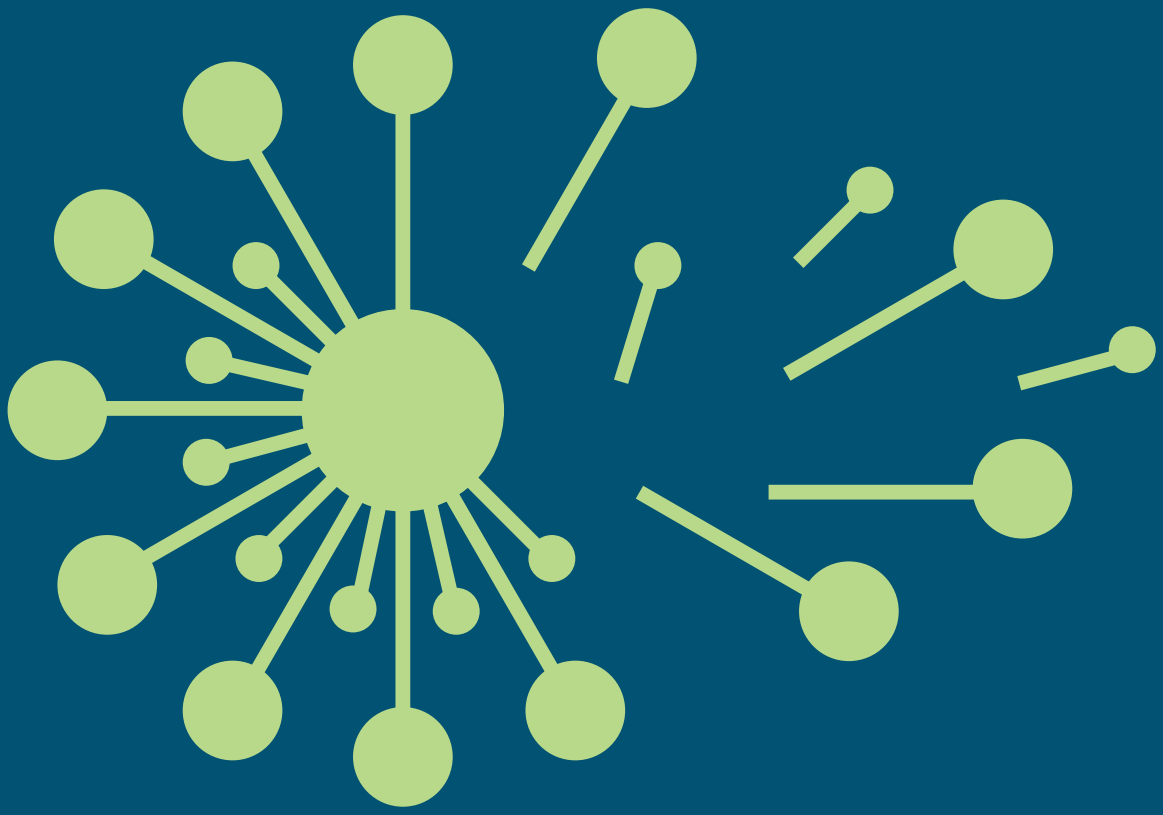
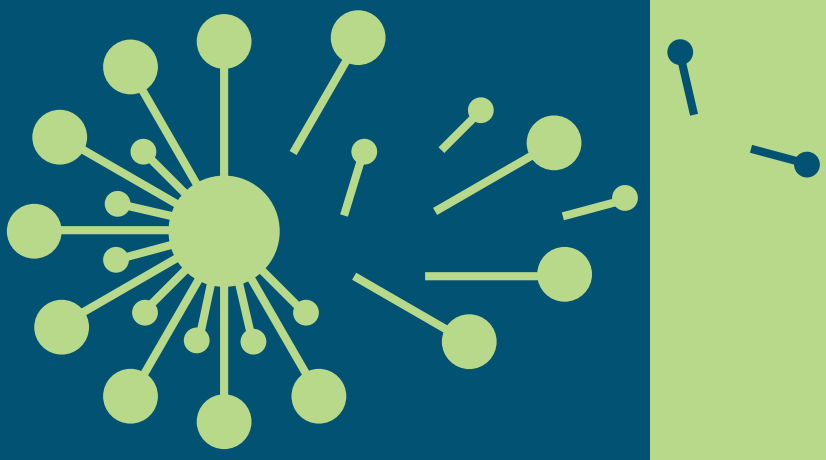


Genome editing and human reproduction

NUFFIELD COUNCIL ON BIOETHICS



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Genome editing and human reproduction: social and ethical issues

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The Nuffield Council's terms of reference:

- To identify and define ethical questions raised by recent developments in biological and medical research that concern, or are likely to concern, the public interest;
- To make arrangements for the independent examination of such questions with appropriate involvement of relevant stakeholders;
- To inform and engage in policy and media debates about those ethical questions and provide informed comment on emerging issues related to or derived from its published or ongoing work; and
- To make policy recommendations to Government or other relevant bodies and to disseminate its work through published reports, briefings and other appropriate outputs.

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We are grateful to George Gaskell of the London School of Economics and Political Science for reviewing and advising on our online questionnaire, and to the volunteers who tested it, as well as everyone who participated – their thoughtful responses enriched the discussions of the working party and we expect that they will repay further study.

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Foreword

The capacity to select the traits of our future children has long been a central theme in science fiction writing, often solemnly warning of the moral dangers associated with doing so, even when undertaken with the best of intentions. The discovery of DNA, the so-called 'code of life', pointed the way towards the scientific avenue through which deliberate intervention to select for desired human traits of future children might be brought about. Yet even after DNA was discovered, the prospect of doing so has remained purely speculative: we simply lacked the scientific knowledge and tools to attempt such a feat. However, as the Council's 2016 report *Genome editing: an ethical review* observes, the development of genome editing techniques has been game changing for research across the biosciences, particularly since the emergence of the CRISPR-Cas9 system in 2012, which enabled precisely targeted alterations to DNA sequences in living cells. As a result, deliberately intervening in the human genome for the purposes of selecting traits of future children has now become a real and distinct possibility. The central question which this Report sets out to address is whether such interventions would be ethically acceptable. Our conclusion is that interventions of this kind to influence the characteristics of future generations could be ethically acceptable, provided if, and only if, two principles are satisfied: first, that such interventions are intended to secure, and are consistent with, the welfare of a person who may be born as a consequence, and second, that any such interventions would uphold principles of social justice and solidarity – by this we mean that such interventions should not produce or exacerbate social division, or marginalise or disadvantage groups in society.

In order to arrive at this conclusion, our approach begins by asking: what is the societal challenge for which deliberate attempts to edit the human genome in the context of reproduction might respond? Put differently, we ask (somewhat more crudely), why might heritable human genome editing be understood as a valuable and worthwhile response to a societal problem? The answer offered in this report centres on the reproductive choices of prospective parents and the preferences they may express for their future child. In the most obvious cases, this may be to take steps that will reduce the prospect of their future child inheriting a genetic disorder. But there is potential for genome editing to be used in a wider variety of more common circumstances, and for a wider range of purposes that may be unrelated to the avoidance of medical diseases or disorders. Our view is that the two guiding principles that condition the ethical acceptability of genome editing in the context of reproduction should orient ethical evaluation and are applicable to the full range of potential motivations for wishing to undertake such interventions. In the UK, genome editing for reproductive purposes is currently unlawful. We make several recommendations concerning how deliberate interventions into the human genome should be governed, including recommendations concerning what we think is needed prior to any move to amend UK legislation to permit heritable genome editing. In particular, we conclude that no such change should be broached without consideration of whether it can be ensured that any proposed use would conform to these two ethical principles: the principle of the welfare of the future person and the principle of social justice and solidarity. Although the prospect of such a move remains a very long way off and, indeed, might never arrive, we nevertheless emphasise the need for broad, inclusive societal debate concerning the desirability of such interventions to take place sooner rather than later, in order to produce an understanding of the public interest, and for engagement with other countries and international organisations to help develop international norms for the law and governance of genome editing.

When I was asked to take on the role of Chair in the summer of 2016, my initial instinct was to decline the invitation. Because the moral acceptability of intervening in the human germ line with the aim of affecting the traits of future children is highly contested, often engaging deeply held views, I was acutely aware that, whatever conclusions the working party arrived at, some people were bound to oppose and even abhor them. In other words, I recognised that by taking up the role, I would be taking up something of a poisoned chalice. At the same time, I had not arrived at my own personal view about the ethical acceptability or otherwise of heritable genome editing, particularly in light of my own experience of the unique and extraordinary role of being, and the process of becoming, a parent of children created within my body to whom I had given birth. My reluctance to take up the role of Chair was partly, perhaps, a product of recognising that, in order to arrive at a position, one must inevitably confront some intractable and insoluble questions including, among other things, questions concerning the significance and sanctity of what it means to be human, and how properly to comprehend the unique character of the parent-child relationship. Accordingly, intentional attempts to intervene in the human germ line might affect our responses to those questions, and to that meaning and character, for good or for ill. Nevertheless, I overcame my initial reluctance to accept the role of Chair, recognising - as I have often counselled my students – that the difficulty, complexity and contestability surrounding a set of questions are not good reasons to shy away from attempting to grapple with them. This is all the more so when the questions are real, important and can have tangible and profound consequences for the lives of individuals and for society more generally.

I have been extraordinarily honoured and humbled to chair the working party that produced this report. The process required to produce it was long, arduous, intellectually complex yet enormously rewarding. It necessitated interdisciplinary engagement and dialogue that was both indispensable and deeply challenging. It has been an immense privilege to work with my colleagues on the working party to whom I am sincerely indebted: not only for their time, dedication, commitment, and expertise, but above all for their attitude and the spirit of inquiry and cooperation through which we have collectively found a way to see past our differences and potential impasses in order to find a productive way forward. The working party has received the benefit of the experience, expertise and views from a great many individuals, organisations and other stakeholders. I wish to express my thanks to all of them for generously sharing their time and insight, as well as to all those who responded to our public call for evidence and who responded to the questionnaire which we publicised on-line in order to help us gauge the range of responses to different contexts and purposes for which genome editing in the reproductive context might be contemplated. Thanks are also due to the Nuffield Council, and particularly its Executive and especially to Anna Wilkinson for her excellent research assistance and support, and to Hugh Whittall for his sage advice and insight at various points throughout the inquiry. I have been continually impressed with the exceptional quality of research and administrative support provided by the Executive, despite the long and demanding hours that this necessitated from time to time. Finally, it is to Pete Mills, to whom I owe the largest debt of gratitude. Without the sheer breadth and depth of his expertise and insight, his stewardship of the inquiry's timetable, his tireless good humour and professionalism, and his willingness to take on the daunting and unenviable tasks of its drafting, revision and reworking, this report could not have been produced.

Karen Yeung, July 2018

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Terms of reference

1. To examine ethical questions relating to the attempted influence of inherited characteristics in humans, in the light of the likely impact of genome editing technologies.

2. To review relevant institutional, national and international policies and provisions and to assess their suitability in the light of the ethical questions examined.

3. To report on these matters and to make recommendations relating to policy and practice.

Table of Contents

Summary

1. This report was prompted by the rapid emergence of a new biological technique and the prospect of a new reproductive technology built upon it, one that could give unprecedented power to intervene in the human genome. It was also prompted by the emergence of a new kind of human self-understanding through research into the role and function of the human genome. This new knowledge and understanding complicates how people relate to themselves, their families and others in their social world. The report's aim is to examine how, in some contemporary societies, including the UK, people with new knowledge and new opportunities, can arrive at decisions that bring the deep structure of social morality into question and potentially redefine the shared moral landscape. Its aim is also to suggest how to move ahead from there, taking a course that is plotted through careful ethical reflection.

2. This summary gives a brief overview of the main content of the report. The conclusions and recommendations developed in the report are brought together in the final chapter (Chapter 5).

Chapter 1 – The landscape

3. The first chapter describes, in outline, the state of current scientific knowledge about the human genome, particularly the role the genome plays in the inheritance of characteristics. It describes the effect of this knowledge on the understanding of relationships between the inherited genome, the state of embodiment and the freedoms of individuals. It describes the mechanisms and significance of human genetic variation, its importance to the human species and how variations can lead, in certain conditions, to states of ill-health and disadvantage.

4. The chapter describes current arrangements for access to individual level genetic information and clinical diagnosis through genetic testing, particularly within the context of health services in the UK. It describes how families with genetic conditions associated with states of disease and disability, in particular, may engage with those services. The chapter suggests that genomic information constitutes a new layer of knowledge, putting individuals in an unprecedented 'epistemic position' with regard to how they understand their embodiment, and their relationships with others and with the environment in which they live. Along with this knowledge come new kinds of responsibility to act or not act on that information, within the terms of that understanding, and according to the opportunities that are available.

5. The chapter describes the options that might be available to those in such an epistemic positon to exclude or include specific genetic variants in their offspring. Only some of these options enable them to do this while at the same time having a child that is genetically related to both parents. The options for maintaining this genetic link include selective techniques (notably preimplantation and prenatal genetic testing), in which genetic information from tests carried out on an embryo or fetus is used to decide whether to continue a pregnancy or whether to transfer an embryo (possibly excluding other embryos). Other potential options, on which the report focuses especially, include modifying an embryo or the cells from which it is formed by techniques of genome editing, in order to ensure that a future child has the selected genetic variants.

6. While people's motives for having children are personal and may be obscure, the 'epistemic position' and the social and technological circumstances mean that the way in which people act requires a decision, often involving complex deliberation. The chapter concludes with an examination of what is at stake in the decision to use genetic reproductive technologies to have genetically related offspring and, at the same time, to include or exclude certain characteristics. The complexity of this framing requires an ethical response that takes into account the interaction and interdependence of the interests of parents and offspring, and the responsibilities to and of society to secure or to restrain these interests.

Chapter 2 – The horizon

7. Chapter 2 expands the focus from individuals confronting personal decisions in the light of certain kinds of background knowledge and specific information, to the way in which the technologies by which they are surrounded bring them into the position where they can express their moral agency in different ways. The chapter falls into two halves, the first dealing with scientific and technological context and the second dealing with the non-technical (social) context.

8. The chapter first describes recent development of genome editing systems, in particular systems based on CRISPR-Cas9, and its use in human embryo research. It identifies a number of possible strategies that might make use of genome editing to influence or secure inherited characteristics in offspring. These include modifying gametes prior to fertilisation and modifying early embryos *in vitro*. It describes how further developments in genomics might expand the repertoire of potential uses for these techniques.

9. The second part of the chapter explores the conditions and dynamics according to which innovation, diffusion and further expansion of the use of genome editing technologies might take place. While it is not possible to predict the course of development, the chapter identifies a number of potential 'use cases' for heritable genome editing interventions. Among them are very rare cases of inherited genetic conditions where the chances of having a genetically related child without the condition are slight, and cases where predisposition to complex diseases cannot be reduced significantly by selective techniques. The chapter then looks at the drivers and conditions that could lead to a diffusion of heritable genome editing for closely and more remotely related reasons.

10. The chapter then draws attention to the conceptual, institutional, regulatory and economic factors that may determine whether and how genome editing technology enters into use, and the social and moral norms that will affect its acceptability. It notes that technology and the social environment in which it develops can influence each other reciprocally, such that the use of technology may secure, embed or transform the conditions by which it is received in that social context. Reflecting on these processes helps to identify sites and opportunities for more constructive governance, prioritisation and control, including the role that moral judgement might play.

Chapter 3 – Ethical considerations

11. Chapter 3 proposes an approach that draws on the discourse of human rights to address the complex entanglement of interests, moral claims and ethical principles engaged by prospective heritable genome editing technologies. It explores ethical arguments relating to uses of genome editing in relation to three kinds of interest, those of the individuals involved, of the society in which they live and of human beings in general.

12. The first section, on considerations relating to the individuals directly involved (principally the prospective parents and their future offspring), takes forward the discussion of situated decision making from Chapter 1. The chapter begins by considering the kinds of claim that arise from the interests of prospective parents in certain circumstances (their desire to have a genetically related child and the information they have about the likelihood that any child they have will have a certain genetic condition). Alongside the prospective parents' interests are set considerations about the welfare of the future person. A principle is proposed to give proportionate weight to the interests of the future offspring, recognising the interdependence of the interests involved.

> **Principle 1: The welfare of the future person**
>
> Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.

13. The second section focuses on considerations relating to others in society, i.e. those who may be collaterally affected by the use of hereditable genome editing interventions or by the adoption and diffusion of such practices, and of society as a whole. It considers how the exercise of individual interests shapes the context in which others must pursue their own interests. Consideration is given to the implications of potential shifts in moral norms (e.g. those governing the acceptability of reproductive interventions) and the consideration owed to those whose positions in society may be collaterally affected, such as those with genetic conditions that may be the target of interventions. A principle is proposed to ensure that proportionate weight is given to the interests of all, recognising the fact that individuals regulate their common life according to an integrated system of social and moral norms.

> **Principle 2: Social justice and solidarity**
>
> The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.

14. The third section focuses on considerations relating to future generations and to humanity in general. This section considers the relationship between 'the human genome' and human rights, and the nature of the alleged harms against which several international legal instruments are supposedly levelled. Although there are many suggestions in the law and in academic literature of a connection between the possession of a human genome and the enjoyment of human rights (or the possession of human dignity), such a connection does not appear necessary. The section concludes by addressing the question of directing human evolution and the possibility that genome editing may create significant inequalities or divisions among humans, or even lead to a divergence between those who have, and those who have not, been born following genome editing.

15. The chapter concludes that none of the considerations raised yields an ethical principle that would constitute a categorical reason to prohibit heritable genome editing interventions.

Chapter 4 – Governance

16. Chapter 4 takes the conclusions arrived at in Chapter 3 and considers how the principles proposed could guide the formulation, amendment and application of practical governance arrangements, including legal, regulatory and professional governance measures.

17. The chapter reviews current legislation in the UK, Europe and internationally, as well as other significant jurisdictions (including the US and China), drawing attention to similarities and differences of approach. It identifies the different levels and scope of regulation and the challenges of a global situation in which the national legislation of different countries expresses different ethical values, but in which people, knowledge and skills are internationally mobile and where inequalities of wealth and access to technology persist. It draws attention to the human rights framework underpinning international law as providing a basis on which some elements relevant to heritable genome editing interventions could be further elaborated. It concludes that there is no prohibition in European community or international law that would make heritable genome editing interventions unlawful.

18. The chapter surveys UK legislation, noting that it currently prohibits heritable genome editing interventions. It also notes the richness of other forms of regulation and soft governance, including the role of learned and professional societies and institutions that contribute to fostering public debate and democratic participation.

19. The chapter makes concrete recommendations for research organisations in the natural and social sciences concerning, respectively, the development of standards of safety and clinical feasibility, and the investigation of the welfare implications of genome editing. Recommendations are made to the UK Government about the possible revision of current legislation to permit heritable genome editing interventions. The chapter makes clear that no move should be made to make heritable genome editing interventions lawful until there has been an opportunity for broad and inclusive societal debate, and it recommends the establishment of a new institution or commission to foster debate in this and related areas. Furthermore, any legislative change should be preceded by consultation with those who might be negatively affected and should not take effect until measures to monitor the social consequences and to mitigate any adverse effects are in place.

20. The chapter also makes recommendations to governments in the UK and elsewhere regarding the fostering of relevant public debate and the development of international human rights instruments to ensure a workable consistency of national approaches, accepting the need for margins of appreciation among members of the international community. States should, in particular, give consideration to ensuring that intellectual property rights are exercised in the public interest and that adequate protections against unfair discrimination are in place.

21. Finally, the chapter makes specific recommendations with regard to the regulation of heritable genome editing interventions, should their use be approved in the UK. These include that their use should not be permitted until risks of adverse outcomes have been thoroughly assessed, and then only on a case-by-case basis, licensed and regulated

under the system currently overseen by the HFEA, and within the context of a carefully monitored study, with comprehensive follow-up arrangements in place.

Chapter 5 – conclusions and recommendations

22. The final chapter draws together the conclusions and recommendations from the report, setting these out in a concise summary of the overall line of argument.

Introduction

The present report comprises part of a programme of work that began for the Nuffield Council on Bioethics with the commissioning of a background paper on genome editing in 2014. The background paper was followed by a scoping workshop with invited experts in April 2015 to identify the most important challenges raised by genome editing that the Council should address. In the light of this discussion, the Council proposed (unusually) a programme of work in distinct stages. The first stage culminated in the report *Genome editing: an ethical review*, which was published in September 2016. This was intended to provide an examination of conceptual and descriptive questions relating to genome editing and of its impact on research to date, to map the broad landscape of potential applications and to identify and prioritise the moral and societal questions it raised.[1] The second stage of work was intended to result in further, more narrowly focused outputs that relate to a clearly demarcated field of application or an otherwise well-characterised set of challenges, containing normative conclusions and recommendations. The present report is the first of these 'stage 2' reports.[2]

The different approaches taken in the two stages of the Council's work are intended to negotiate a potential danger that was identified in an earlier Nuffield Council report, which set the stage for ethical consideration of emerging biomedical technologies such as genome editing.[3] The danger is that of narrowing the consideration of the challenges confronting societies around the promise of particular prospective technologies rather than considering the potential 'solutions' in the broader context of other approaches. Equally, there is a danger of focusing only on questions of innovation and not considering the further directions that technology use might take and what it might be like to live in a society in which such technologies were available. Thus, whereas the first part of our work began with the development of a new scientific technique and considered the ends to which its potential practical uses might extend, this second part of our work looks at the situation the other way around. We therefore begin with some of the challenges facing human societies and then consider what role heritable genome editing interventions might have in the context of other actual and possible responses to those challenges.

Grounding our inquiry

From the outset, to guide its work, the working party has adopted as a maxim the injunction to 'start with reality'. This has come to mean three things, all of which have been equally important in this project. The first is to begin with an accurate understanding of the technical potential and limitations of the techniques of genome editing (and enabling technologies) and a realistic appraisal of current research, rather than being swept along by hyperbole. To stipulate this is not, however, to deny our interest in where genome editing might lead in future. Indeed, to the large extent that the project is concerned with matters of public policy, the working party's reflections have been orientated by a reflection on the possible futures that such policies may help to shape.

The second sense in which the report 'starts with reality', then, is to begin by identifying the most proximate and likely applications of heritable genome editing interventions (taking into

[1] Nuffield Council on Bioethics (2016) *Genome editing: an ethical review*, available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf.
[2] Work on a second report on genome editing in relation to farmed animals is in progress at the time of publication.
[3] Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf.

account the strength of the supporting moral case). It is from them that we can then proceed to consider how the uses of the technologies and the arguments that support them might be developed and extended. This means not considering each possible use of genome editing in isolation, but considering the connections and distinctions between them, in particular what happens if and when heritable genome editing interventions enter clinical use. By hypothesis, the conditions for this to occur are likely to be complex and interdependent.

The third sense of our maxim is therefore to recognise that any use of technology is always already embedded in a context of social and political realities, as well as depending on a variety of contingent and co-evolving technological, economic, practical, epistemic, legal and moral conditions. This means that we have to appreciate the development, introduction and diffusion of technologies as subject to human interests and desires, economic conditions, scientific and corporate culture, the priorities of funders, the structures of institutions, the plurality of public opinion, the mechanisms of legal change and the priorities of policy makers. In other words, the relationship between a technical innovation and the context in which it appears is complex, dynamic and contains many interdependencies. While the possibility of innovation may be shaped by prevailing social and moral norms, we recognise that these norms may equally adapt to the technologies in use in society.

A note on terminology

It has proved unfeasible, in writing about cutting-edge scientific developments, to avoid completely the use of certain technical terms. We have retained terms for technical concepts (such as 'genome', 'DNA' and 'norm') where it is easier to do so than to express them in another way. To help the general reader, we have offered an explanation of the meaning of such terms at their first occurrence, and we have included a glossary at the back of the report that may be consulted at any time. We have also striven to reduce, so far as possible, the use of technical concepts from the humanities and social sciences, which are often doubly deceptive as a result of being disguised as familiar terms from everyday speech. We have tried to anticipate this and to explain any terms that might give rise to ambiguity.

Our task has been made doubly difficult because of the absence of agreed, common terminology and the difficulties that this presents for ethical discussion. This is inevitable in a rapidly expanding field that engages researchers and commentators using a variety of natural languages and without an authoritative body to determine which should be used. We refer to 'genome editing' in preference to 'gene editing' (which is also common) because we do not intend the concept to be restricted only to the modification of genes, but to encompass modifications of the epigenome and regulatory sequences as well, and also because such changes may affect the organism-wide functions of the genome. We generally refer to the range of genome editing practices of interest in this report as 'heritable genome editing interventions' (rather than, for example, 'germ line genome editing').

Furthermore, we are especially conscious that language can be morally loaded and often embeds a way of seeing the world or encourages particular ways of responding to phenomena. In our 2016 report *Genome editing: an ethical review*, we called attention to how this works through identified 'confusing terms', 'contested concepts', 'inconsistent framings' and 'contending imaginaries'.[4] For the present report, in describing differences at the molecular level, we have generally preferred the terminology of 'genetic variation' to that of 'genetic mutation' or 'genetic defect', although all of these continue to occur in relevant literatures. 'Genetic endowment' is used to describe what is inherited by each organism from its biological

[4] Nuffield Council on Bioethics (2016) *Genome editing: an ethical review*, available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf.

progenitors. At the publicly observable level, we have generally preferred 'characteristics' to 'traits' or 'features' where context permits. States of embodiment that are related to a person's genetic endowment under given environmental conditions at a particular time have been rendered as 'conditions', which include genetic diseases and disabilities ('disorders') as they are commonly described in medical discourse.

Value concepts are fundamental to our work and, in this report, we use two distinct terms to refer to value concepts: 'ethical' and 'moral'. Many people use these almost interchangeably, but we have tried to observe a basic distinction between usage that refers to personal or social norms of right and wrong conduct ('moral') and usage that purportedly relates to some source of value beyond convention and prudence ('ethical'). We acknowledge, however, that there is substantial disagreement about the meaning of the terms.[5] 'Bioethics', however, according to our understanding, is an interdisciplinary activity (that draws not only on formal knowledge, but also on folk morality and cultural understanding) that involves the inclusive, deliberative and reflective examination of how conduct should be governed (especially at the level of public policy, and therefore for political communities) insofar as it relates to biomedicine and biotechnology.

Finally, the reader will find frequent occurrences in the report of the first person plural pronoun ('we'). This is not an attempt to appeal to an authoritative, but contestable and indistinct, shared identity, such as 'we in Britain'. Rather, we use it because this has been an engaging inquiry, so when we advance a particular thought or conclusion, instead of referring to ourselves in the third person (as, for example, 'the working party' or 'the Nuffield Council') it has seemed more appropriate to put ourselves into the frame as the authors of those points.

[5] In the sense it had for the ancient Greeks, 'ethics' was the branch of knowledge dealing with matters of character and right conduct. It has come to refer to the proper standards of conduct for professional groups and activities ('business ethics', 'clinical ethics', 'research ethics', etc.). 'Ethics' (or 'moral philosophy') is also the term used to describe one of the main branches of philosophy, the one that deals with questions of value and human conduct. Ethics concerns accounts of why certain actions are right or wrong and is usually divided into 'applied ethics', which deals with first-order questions such as what an agent should do in a given situation, and 'metaethics', which deals with second-order questions about, for example, what it is that makes a particular recommendation to such an agent right.

Chapter 1

The landscape

Chapter 1 – The landscape

Chapter overview

This chapter describes, in outline, the state of current scientific knowledge about the human genome, particularly the role the genome plays in the inheritance of characteristics. It describes the effect of this knowledge on the understanding of relationships between the inherited genome, the state of embodiment and the freedoms of individuals. It describes the mechanisms and significance of human genetic variation, its importance to the human species and how variations can lead, in certain conditions, to states of ill-health and disadvantage.

The chapter describes current arrangements for access to individual level genetic information and clinical diagnosis through genetic testing, particularly within the context of health services in the UK. It describes how families with genetic conditions associated with states of disease and disability, in particular, may engage with those services. The chapter suggests that genomic information constitutes a new layer of knowledge, putting individuals in an unprecedented 'epistemic position' with regard to how they understand their embodiment, and their relationships with others and with the environment in which they live. Along with this knowledge come new kinds of responsibility to act or not act on that information, within the terms of that understanding, and according to the opportunities that are available.

The chapter describes the options that might be available to those in such an epistemic positon to exclude or include specific genetic variants in their offspring. Only some of these options enable them to do this while at the same time having a child that is genetically related to both parents. The options for maintaining this genetic link include selective techniques (notably preimplantation and prenatal genetic testing), in which genetic information from tests carried out on an embryo or fetus is used to decide whether to continue a pregnancy or whether to transfer an embryo (possibly excluding other embryos). Other potential options, on which the report focuses especially, include modifying an embryo or the cells from which it is formed by techniques of genome editing, in order to ensure that a future child has the selected genetic variants.

While people's motives for having children are personal and may be obscure, the 'epistemic position' and the social and technological circumstances mean that the way in which people act requires a decision, often involving complex deliberation. The chapter concludes with an examination of what is at stake in the decision to use genetic reproductive technologies to have genetically related offspring and, at the same time, to include or exclude certain characteristics. The complexity of this framing requires an ethical response that takes into account the interaction and interdependence of the interests of parents and offspring, and the responsibilities to and of society to secure or to restrain these interests.

Introduction

1.1 In sexually reproducing organisms, the genome of each individual is composed of approximately one half that is provided by the biological mother and the other half provided by the biological father. During the process of reproduction, genetic material from the parents combines to produce the unique genome of their offspring. Reproduction is therefore a key moment at which different genetic variations can be included or excluded, or combined. This has consequences both for the species and for

the individual, as it allows for the evolution of advantageous traits and provides each person with a unique genetic identity.

1.2 The human genome is contained in 23 pairs of chromosomes (22 autosomes and 1 pair of sex chromosomes) in a sequence of paired chemical bases that are held together in the long molecules of deoxyribonucleic acid (DNA) that are present in almost all the cells of the body.[6] The genome is the complete set of genes – regions of the DNA molecule of varying length that usually encode proteins that perform distinct biological functions – together with interspersed non-coding regions that regulate when the genes are expressed. People usually have two copies of most genes.[7] Genes can have different forms, called alleles, and differences between alleles are not uncommon. In addition to the DNA sequence, the genome has associated chemical elements (called the epigenome) that have distinct biological functions and can be modified by the environment.[8]

1.3 Although all people have similar sets of genes, no two people have exactly the same genome.[9] Even the genomes of 'identical' (monozygotic) twins may differ owing to errors in DNA replication and somatic mutations, as well as acquired differences in their epigenomes. Some of the genomic differences between people produce differences in their appearance or in their physiology (known as their 'phenotype'), while others have no observable effects. Although genomic differences can be highly significant for the expression of disease-related and other characteristics, many of the differences between people that are observable or medically significant arise from the combined effects of genetic, environmental and biographical factors. Environmental factors, including some viruses, can cause changes in genes that may, for example, increase susceptibility to cancers.

1.4 Sometimes, inherited genomic variations can result in disease or confer predisposition to disease.[10] This usually comes about due to small changes in the genome, which may be transmitted to future generations.[11] These changes can affect the production of proteins in cells, as well as the regulatory regions of genes or genes that encode a ribonucleic acid (RNA) product. There is an enormous range of ways in which genetic

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6 For an elucidation of technical terms, please refer to the glossary at the end of this report. All cells in the human body (excepting red blood cells, which have the specific purpose of transmitting oxygen around the body) contain DNA. This is ordinarily found tightly wound in the 46 chromosomes in the cell nucleus; small amounts of DNA are also found in mitochondria (subcellular organelles).

7 Not everyone has two copies of every gene. X-linked diseases affect males because they have only one copy of the X chromosome. People with Down's syndrome have three copies of chromosome 21 in most or almost all of their cells.

8 The basic biology of genome editing is described in more detail in our earlier report, Nuffield Council on Bioethics (2016) *Genome editing: an ethical review,* available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf. As we indicated in that report, when we use the term 'genome editing', we refer also to precise, targeted changes to the epigenome through, for example, modification of histone and methyl groups that regulate gene expression, as well as the sequence of bases that are ordinarily understood to comprise the genome.

9 The Human Genome Project aimed to produce a reference genome and published an initial, incomplete version in 2003. See: International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome *Nature* **409(6822)**: 860–921; Collins FS, Green ED, Guttmacher AE and Guyer MS (2003) A vision for the future of genomics research *Nature* **422**: 835–47.

10 It is estimated that all people carry a small number of lethal mutations inherited from one parent that do not manifest because they also carry a normal copy inherited from the other parent.

11 Damage to DNA occurs continually and has many causes, including radiation exposure (e.g. X-rays or UV light), atmospheric chemical toxins (e.g. polycyclic aromatic hydrocarbons from vehicle exhaust or cigarette smoke) or infection (e.g. with HIV). The cells of the body contain mechanisms to repair the damage, but in some cases it may lead to cell death or to the replication of an altered genome, which can be a cause of disease in the organism. Some epigenetic changes can be passed down to people's offspring.

disorders manifest in affected people.[12] Inherited genetic conditions account for a range of differences that include life-limiting conditions such as Duchenne muscular dystrophy and cystic fibrosis. Genetic conditions are furthermore significant causes of infertility, pregnancy loss and neonatal death. Additionally, even the same genetic mutation can range widely in the way that it is manifested in the people affected (their 'phenotype') and the consequences that this may have for the length or quality of their lives. This is because the function of some genes can be modified by other genes, as well as by environmental factors. In the case of 'single gene disorders', it is therefore possible that multiple variants in the same genome affect the associated phenotype. These are sometimes referred to as 'modifier genes'.

1.5 In this chapter, we consider how understanding of the effects of genetic variation has developed, particularly of how certain genetic variations lead to states of disease and disability. We consider how, though it affects people differentially, controlling genetic variation can be understood as a 'societal challenge' (i.e. a challenge that we face collectively). We conclude by considering how we should understand this challenge and the moral significance attached to it in order to clarify what is at stake when we think about the prospect of using new techniques to make targeted changes to the genome in the context of human reproduction.

Genetic disorders

Single gene disorders

1.6 Over 10,000 single gene disorders have been identified, which are associated with an alteration in a region of a single gene that affects the biological function of that gene product.[13] Individually, single gene disorders are usually rare, but collectively they affect at least one in every hundred people born worldwide.[14] Because they can be inherited and because of the way humans have evolved, migrated and mixed or, in some cases, become geographically isolated, some genetic disorders tend to be associated with certain ethnic groups. An example is the blood disorder beta thalassaemia, which occurs more commonly among people of Mediterranean origin; another is sickle cell disease, which is more prevalent in Afro-Caribbean groups. Perhaps one of the most widely known single gene disorders in the UK is cystic fibrosis, which arises in children of parents who each have an altered copy of the cystic fibrosis transmembrane conductance regulator gene when the child inherits both mutated alleles. While many genetic disorders are now well understood, many rare genetic disorders have not yet been defined in terms of the genetic mutation responsible.

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[12] Proteins have a large range of different roles in the organism. They typically depend for their production on many genes and a gene can be involved in the production of many proteins. They include structural proteins, enzymes that carry out a specific activity (such as metabolising glucose), hormones that coordinate processes between different parts of an organism, carrier proteins that transport chemicals such as oxygen (haemoglobin) and antibodies that protect the organism from infection. 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'.

[13] We use the term 'disorder' here to refer to what are variously referred to as 'diseases' and 'disabilities'. There are many genetic conditions that do not necessarily entail treatment but may be treated when medicalised (e.g. deafness, achondroplasia). A genetic disorder is therefore a subset of genetic conditions that give rise to a wide range of characteristics. The distinction between disease and disability is a problematic one see: Scully JL (2004) What is a disease? *EMBO Reports* **5(7)**: 650–3. The use of these descriptions is discussed further in Chapter 3 below. There are estimated to be over 10,000 diseases that are caused by mutations in a single gene, affecting millions of people worldwide. See: Online Mendelian Inheritance in Man (2018) *An Online Catalog of Human Genes and Genetic Disorders,* available at: https://www.omim.org/ .

[14] Data relating to the prevalence of genetic disease in populations are poor and vary hugely from one population to another. Furthermore, information in this area is changing rapidly as a result of prenatal screening and diagnosis.

1.7 Disruption of the function of any given gene may be due to many different types of mutation. For example, the most common mutation in cystic fibrosis is a three-base pair deletion that leads to the protein product failing to fold into the proper shape to carry out its biological function.[15] While many mutations are limited to a single base pair, other genetic diseases may involve the deletion, insertion or rearrangement of longer sections of DNA and involve several genes.[16] Diagnosing the underlying genetic basis of a condition is therefore often a case of tracking down the specific mutation in the patient, usually in the context of inheritance through their biological family.[17] Single gene disorders are not always inherited, however, and can arise spontaneously in children of apparently healthy parents.

1.8 Most inherited single gene disorders arise in statistically predictable ways following sexual reproduction. Where the mutations are located on one of the 22 autosomes, these may be inherited in either a dominant or a recessive pattern. Other conditions may be associated with the sex chromosomes (either recessive or dominant).

Box 1.1: Patterns of genetic inheritance

Single gene disorders are sometimes called 'monogenic' disorders or 'Mendelian' disorders, after the Austrian monk, Gregor Mendel, who first described the patterns of inheritance of genetic characteristics in the 1860s.

Autosomal dominant conditions
In the case of an autosomal dominant condition, statistically, 50 per cent of the offspring of an affected parent will inherit the mutated allele.[18] An example of an autosomal dominant condition is neurofibromatosis type 1, in which nerve tissue tumours form in the skin, brain and spinal cord.

Autosomal recessive conditions
In the case of a recessive condition, for a person to be affected, two mutated alleles need to be inherited, usually one from each parent, where both parents are unaffected carriers of the condition. In this situation, 25 per cent of offspring will be affected, 50 per cent will be unaffected carriers and 25 per cent will be neither affected nor a carrier. If only one parent carries a recessive mutation, 50 per cent of the offspring will be unaffected carriers and 50 per cent will not inherit the mutation. In this case, the mutation may persist for a long time in outbred populations without the disease phenotype appearing. An example of a recessive condition is sickle cell disease, which causes an abnormality in the red blood cells that makes them adopt a rigid 'sickle' shape, which can block small blood vessels and lead to anaemia.

Sex-linked conditions
Females who inherit a mutation on the X chromosome are carriers but are rarely affected. When they have children, daughters have a 50 per cent chance of being a

[15] Riordan J, Rommens J, Kerem B *et al.* (1989) Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA *Science* **245(4922)**: 1066-73.

[16] The human nuclear genome comprises approximately 3.2 billion nucleotides divided into 24 linear molecules (the chromosomes), which vary from 50 million to 260 million nucleotides in length. See: Brown TA (2002) Chapter 1, The Human Genome, in *Genomes*. 2nd edition, available at: https://www.ncbi.nlm.nih.gov/books/NBK21134/). Genes in the human genome vary from approximately 0.2 kilobases to 26,000 kilobases. The *DMD* or dystrophin gene, which is affected in the case of Duchenne and Becker muscular dystrophies, occupies approximately 23,000 kilobases on the X chromosome,see: Online Mendelian Inheritance in Man *Molecular Genetics*, available at: https://www.omim.org/entry/300377#molecularGenetics.

[17] Accurate genetic diagnosis will be significant when we consider the possibility of interventions to edit the genomes to restore them to normal ('wild type').

[18] Where one parent is homozygous, all offspring will be affected. Where both parents are heterozygous, 75% of offspring will be affected. In each case, we are speaking about statistical probabilities here rather than necessary outcomes.

carrier and sons have a 50 per cent chance of being affected. When a father has an X-linked condition, his sons will be unaffected as they inherit his Y chromosome and his daughters will be carriers. Examples of X-linked recessive conditions are haemophilia A (a condition that affects blood clotting) and Duchenne muscular dystrophy (which involves progressive muscle weakening). Since males have only one X chromosome, and therefore only one set of X chromosome alleles, they are more likely to be affected by recessive mutations on the X chromosome. There are very few Y-linked conditions, in which all male offspring are affected, an example being Y-linked non-obstructive spermatogenic failure.

1.9 The effect of a genetic mutation on the health of an individual cannot always be predicted. This is a consequence of two factors called penetrance and expressivity. A mutation shows incomplete penetrance when not all people who inherit the mutation have the associated disease. This helps to explain how a mutated allele can be passed down through generations undetected. Expressivity refers to individual variability such as that observed in people with Marfan syndrome, in which affected individuals are usually very tall and thin, but some people have severe symptoms affecting the heart and blood vessels. It is not completely understood how an individual's genes function in the context of their entire genome.

1.10 Social and other non-genetic factors are also important. For many people with genetic conditions, the chances of surviving longer and enjoying a good quality of life are markedly higher for those who have access to advanced healthcare than for those who do not, as well for those who can avoid contributory environmental factors such as smoking, allergens or certain foods. Local healthcare approaches, arrangements for healthcare insurance or dietary preferences (rather than simply the availability of adequate nutrition), as well as the physical environment, can all result in significant variations in health impact.[19]

Complex gene disorders

1.11 Many non-communicable diseases with a high incidence arise as the result of complex interactions between genetic, lifestyle and socio-environmental factors. For this reason, they are often characterised as 'complex', 'polygenic' or 'multifactorial' diseases. Different gene variants (alleles) at multiple locations may be implicated to different degrees in increasing or reducing the risk of any individual person being affected. Heart disease, diabetes, obesity, Alzheimer's disease, multiple sclerosis, Parkinson's disease, asthma, osteoporosis, schizophrenia and some cancers are all examples of diseases in which common gene variants have been implicated as causes, but are insufficient to account for the disease in the absence of other factors.[20] These diseases do not have well-defined patterns of inheritance, although they may cluster in families that share an environment. Complex diseases may have genetic risk factors that are masked by protective factors affecting penetrance.

1.12 Seminal studies by Richard Lewontin in 1972 showed that most human genetic diversity is shared between all populations, with very little difference between geographical groups, although further research has found that the frequency of certain variants in

[19] Phenylketonuria is an inherited metabolic disorder that can lead to a range of symptoms, including developmental disorders and seizures; however, avoiding foods containing phenylamine from infancy effectively removes the risk of these symptoms occurring.

[20] Craig J (2008) Complex diseases: research and applications *Nature Education* **1(1)**: 184.

different groups and geographic populations can vary significantly. Subsequently, the Human Genome Project revealed that the genomes of any two people may typically differ at between 4.1 and 5 million sites.[21] A current challenge is to determine which differences may or may not affect disease susceptibility. (We discuss advances in genome sequencing and the detection of significance through genome-wide association studies in Chapter 2.) Genetic variation is also associated with susceptibility to infectious agents, allergens and response to drugs, including extreme adverse reactions. It is also the likely explanation for the fact that alleles that can be harmful may be protective when the person who inherits them also inherits a different allele (heterozygous). One example is the ability of some people to respond to therapy for hepatitis C virus (HCV) infection. This has been shown to be due to a particular variation in the gene that encodes a type of interferon, which is a first responder to viral infection.[22] The persistence of the recessive sickle cell trait, which causes sickle cell disease when inherited from both parents, appears to be a consequence of its protective effect against malaria.[23] Thus, although it causes serious disease in some cases, elimination of the trait from the population would probably have negative consequences at the population level if malaria were present. The value of genetic diversity is thus not limited to individual well-being, but to the human population as a whole and its susceptibility to disease.

1.13 Although genetic variations, which are conserved throughout an organism's life cycle and, where they are inherited, across generations, may either cause or contribute to human disease, DNA damage that occurs during the course of a person's life can also affect their physiology and therefore their health. Sources of such damage include environmental toxins such as chemicals, oxidative damage, ionising radiation or UV light, viral infection and spontaneous errors in DNA replication during cell division. These can be encountered in a variety of everyday situations (such as exposure to sunlight and pollution) and through common behaviours (such as smoking). While DNA damage is highly toxic and therefore targeted for repair by the cell, errors may accumulate in the organism's tissues and give rise to tumours. Such errors are not heritable unless they occur in the 'germ line' (i.e. the cells that give rise to the sperm and eggs).

The benefits of genetic variation

1.14 Genetic variation involving the accumulation of random mutations followed by outbreeding has benefits at the level of the species, allowing slow, evolutionary adaptation to the natural environment and to other factors such as prevalence of disease agents. However, in the human population today, evolutionary adaptation to the natural environment may appear to be of much less significance owing to the timescale and factors such as medical care and geographical mobility.[24] Nevertheless, it is difficult to overstate the importance and value of genetic variation.

1.15 Even when genetic diversity is retained silently and is unexpressed (as is the case with many recessive genetic conditions) it can have biological benefits as a reservoir of variation that may be available for preferential selection in different environmental conditions (e.g. if climate change results in an extension of the range of latitude in which

[21] The 1000 Genomes Project Consortium (2015) A global reference for human genetic variation *Nature* **526 (7571)**: 68-74.
[22] Lu YF GD, Angrist M, and Cavalleri G (2014) Personalized medicine and human genetic diversity *Cold Spring Harbor Perspectives in Medicine* **4(9)**.
[23] AC Allison (1954) Protection afforded by sickle-cell trait against subtertian malarial infection *British Medical Journal* **1**: 290-94.
[24] If the pathogen is no longer present, such as North Americans from Afro-Caribbean backgrounds carrying the sickle cell mutation in haemoglobin now living in malaria-free regions, heterozygosity may confer no advantage, while homozygotes will be affected by sickle cell disease.

tropical diseases occur). If it is expressed as physical diversity, genetic variation can also lead to social benefits. For example, it may encourage people to appreciate difference and care for and respect others, whereas having less diversity might make the lives of those with less common genetic traits still more marginal.

1.16 People also value their own embodiment in different ways. Some people affected by genetic conditions that are viewed negatively by others value their condition and would not want to have their condition altered or to have been born without it.[25] This may be because our experience in our own bodies is an important part of how we see our identity (we will discuss this further in Chapter 3). Although this is unlikely to be the case for many diseases, such as cancers, it may be so for a small range of conditions and, indeed, some people may want to continue with their family incorporating a genetic trait that most others may view as a disadvantage (e.g. congenital deafness).[26]

1.17 Particularly, since it has been possible to study genetic variation at the molecular level there has been significant developments in science and technology, stimulating human resourcefulness to address a range of challenges and, collaterally, generating economic value.[27]

The range of human variation

1.18 Advances in genome sequencing technologies and their increasing use are significantly extending our knowledge of genetic variation and its role in human health and functioning. The accumulation of genome data from multiple, parallel sequencing initiatives on the exome (the part of the genome that contains genes having comparatively well-characterised functions) or the whole genome and information about the health and constitution of sample donors are revealing the (perhaps surprisingly high) prevalence of variations that previous studies have associated with particular disease states.[28]

1.19 The findings of genome research suggest two significant things for our inquiry: first, that what is encoded in the genome is only the start of the story of our physiology; and second, that a different combination of factors could have profound physiological consequences for almost any of us. All of us carry a number of risk factors and predispositions to disease, some possibly lethal, which may or may not materialise into disease in us, depending upon the occurrence of a relevant environmental exposure or lifestyle choice. However, a chance combination is always possible through the choice of reproductive partner that could affect the next generation. At the same time, everyone is constantly sustaining genetic damage from the environment, which may affect their eggs or sperm when they come to reproduce. This has implications for what we mean by ‘health’, ‘disease’ or ‘disability’ because it adds another layer of understanding to previous forms of diagnosis. People may have genetic ‘conditions’ with no apparent symptoms; a range of factors that may predispose to future disease or cause varying

[25] Boardman F, Young P and Griffiths F (2017) Population screening for spinal muscular atrophy: A mixed methods study of the views of affected families *American Journal of Medical Genetics Part A* **173(2)**: 421-34

[26] See, for example, BBC (2008) *Is it wrong to select a deaf embryo?*, available at: http://news.bbc.co.uk/1/hi/health/7287508.stm.

[27] See, for example, the foregrounding of genomics in the NHS in Bell J (2017) *Life sciences: industrial strategy – a report to the Government from the life sciences sector,* available at: https://www.gov.uk/government/publications/life-sciences-industrial-strategy.

[28] See: Xue Y, Chen Y, Ayub Q, *et al.* (2012) Deleterious- and disease-allele prevalence in healthy individuals: insights from current predictions, mutation databases, and population-scale resequencing, *American Journal of Human Genetics* **91(6)**: 1022–32; ACMG Board of Directors (2014) ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing *Genetics in Medicine* **17**: 68–9.

levels of susceptibility or robustness in the presence of environmental conditions are brought into play.[29] The understanding furnished by genomics further undermines the possibility of thinking of 'health' and 'disease' as a simple dichotomy and as a way of capturing the range of human states and predispositions.[30]

1.20 This more sophisticated understanding of health and disease is not only a theoretical matter; more practically, increased understanding of genomics can contribute to a change in the way in which responsibility for health is understood to fall on public authorities and especially on individuals.[31] This can come about as a consequence of thinking about health less as a given state of being in the world, than the manageable expression of any number of predispositions and 'risk factors', many of which are already present in the genome. The practical consequences of the diffusion of genomics are, on the one hand, the increasing emphasis in healthcare on prevention and public health and, on the other, the development of increasingly 'personalised' (and therefore differentiated) medicine. This suggests new obligations of public authorities to provide common conditions for all people (good-quality environmental conditions such as air quality and equitably provided healthcare). However, individual genetic variation also raises new questions of individual moral responsibility, such as for choices about how people manage the relationship between their genotype and their environment (e.g. their responsibility to eat a low-cholesterol diet if they have a diagnosed genetic susceptibility to obesity or atherosclerosis).[32] Importantly for our inquiry, moreover, knowledge about genomics raises the question of responsibility on individuals not only for adapting their *own* behaviour and choosing a suitable lifestyle and a suitable material and social environment, but also, potentially, for selecting a genotype that will be expressed in their future children.

1.21 Throughout history, people have sought to secure or avoid having offspring with certain characteristics for both social and personal reasons. They have done so by a range of more or less effective methods that can now be regarded as proxies for genomic selection, including by folkloric methods of sex selection, incest taboos and partner or gamete donor selection based on observable physical attributes. In most cases, their responsibility for the outcome has been largely limited by factors beyond their knowledge or control. Genomic knowledge adds a significant new dimension to this responsibility and genomic technologies place in their hands new and more powerful tools to pursue their reproductive aims.

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[29] Thus, genome editing cannot be about restoring to a state of health because there is no one state that health represents. In a research interview for this project, Dan Goodley, Professor of Disability Studies and Education at the University of Sheffield, said the following: "As soon as one speaks of genetically caused disability or impairment one also has in mind its opposite, which is not having that disability or impairment. It seems to be that in disability studies and in ethical and political debates about medical interventions we have done well in thinking about disability and the kinds of disability we might want to still see in the world – but less unpacking of the hidden references to able-bodiedness, normality and the idea of a valued life worth living". Interview with Dan Goodley, 29 June 2017.

[30] This dichotomy has already been extensively analysed as phenomenologically complex and structured, in some cases to a large extent, by institutional epistemologies; see: Canguilhem G (1966) *Le normal et la pathologique* (trs. Fawcett CR and Cohen RS (1991) *The normal and the pathological* (New York: Zone Books). This genomic blurring of conditions such as 'health' and 'disease' reflects wider sociological challenges to the reductionism of other 'constraining dualities' such as 'body' versus 'mind', 'rational' versus 'emotional' and 'able' versus 'disabled'; see: Annandale E (1998) *The sociology of health and medicine: a critical introduction* (Cambridge: Polity).

[31] In an earlier Nuffield Council on Bioethics report, we identified this as a trend in modern societies towards ever-greater 'responsibilisation' in healthcare, which, along with 'consumerisation', was a key aspect of the 'personalisation' of healthcare in the post genomic age; 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.

[32] This partly explains why the diffusion of genetic testing creates anxieties among insurance companies about 'moral hazard' and adverse selection.

Genetic testing

Clinical genetics

1.22 When a patient presents with a suspected genetic condition, genetics professionals commonly draw a detailed family tree in order to assist in the diagnosis of a suspected genetic condition. However, this can be limited by the rareness of the condition and its survivability, as well as the limited quantity and quality of available information, particularly relating to previous generations. The availability of genetic, DNA-based tests allows definitive diagnoses in some cases, sometimes leading to greater differentiation among cases.[33]

1.23 Genetic testing is used to confirm or exclude a specific genetic disease and to assess the likelihood that someone will develop, or is a carrier of, a genetic disease. The test may be recommended because a person's relative has a genetic disease or they may be tested as a child or adult because of illness or because they are a member of a population subgroup where a specific genetic disease is prevalent and carrier screening is offered. For example, people of Ashkenazi Jewish ancestry are offered screening for a number of disorders, including Tay–Sachs disease. Expanded carrier screening, where carrier status is simultaneously assessed for hundreds of recessive disorders in couples or individuals who do not have an increased risk of being a carrier, can be applied to individuals regardless of their ancestry. Studies have shown that about two per cent of couples carry a single gene variation that could result in a child with a serious genetic disorder. We heard, in evidence, that expanded carrier screening was now a routine part of *in vitro* fertilisation (IVF) procedures in the US and is set to become more common elsewhere. Furthermore, there was a general expectation that panel assays (in which a range of common conditions are tested for at the same time) would, in time, be replaced by whole-genome sequencing.[34]

1.24 While genetic testing for genetic disease or carrier status is often available through health services, the increasing use of genetic testing and, in particular, genome sequencing in mainstream medicine and biomedical research has increased the background of genomic information available. A burgeoning source of genomic data is biomedical research involving genome sequencing from specially recruited participants. The UK's 100,000 Genomes Project, initiated in 2011, is a continuing example, but already looks modest in ambition against, for example, the pharmaceutical company AstraZeneca's proposal to sequence the genomes of two million (eventually 10 million) people and the strategic ambitions of the UK Government and life sciences sector.[35] Research projects

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[33] In evidence, we were told that there has been a dramatic change in clinical practice regarding rare diseases in the three or four years up to 2017. Earlier approaches based on building cohorts with undiagnosed patients only rarely led to specific treatments. With the advent of massively parallel sequencing in 2010, there has been a huge change in capacity to diagnose these rare conditions (from 25% of molecular diagnosis for patients in clinical practice to ~60%), although there remains insecurity on the parts of the patients regarding the implications of the information (i.e. the adequate level of sophistication of a diagnosis in relation to needs such as social security and implications for family members). Genomic technology theoretically allows for an almost 'unbiased' diagnosis of unknown diseases. The impact is also conceptual (e.g. exome sequencing has broadened the understanding of phenotypes rather than contributed to finding new diseases, which in turn contributes to finding or tailoring of therapies; nonetheless, with exome sequencing, only two-thirds of patients receive a genetic diagnosis). Working party fact-finding meeting on genome editing and human reproduction,10 May 2017

[34] Fact-finding meeting on reproductive genetic technologies, 23 March 2017.

[35] See Genomics England (2018) *The 100,000 Genomes project*, available at: https://www.genomicsengland.co.uk/the-100000-genomes-project/; AstraZeneca press release (12 January 2018) *Harnessing the power of genomics through global collaborations and scientific innovation*, available at: https://www.astrazeneca.com/media-centre/articles/2017/harnessing-the-power-of-genomics-through-global-collaborations-and-scientific-innovation-12012018.html; see also the Government-commissioned report Bell J (2017) *Life sciences: industrial strategy – a report to the Government from the life sciences sector,* available at: https://www.gov.uk/government/publications/life-sciences-industrial-strategy.

of this kind show growing promise partly due to advances in data science and massively scalable information technology platforms that can manipulate and explore the resulting massive data sets (so-called big data). As yet, genome sequencing is not the most cost-effective way of obtaining health-relevant genomic information for specific screening, diagnostic or prescribing purposes. However, the falling cost of sequencing, compared to the cost of commissioning tests for specific changes in a short DNA sequence, might change the economic calculation.[36] Sequencing may therefore become much more attractive for routine diagnosis if concerns about individual privacy and the management and communication of incidental, personally or clinically relevant findings can be managed acceptably.[37]

1.25 As well as contributing to the production of general scientific knowledge, increasingly the data (or their implications) circulate back to the individual. One significant incentive to produce genomic data lies in the mutually beneficial convergence between research and healthcare. This is leading to the increasing blurring of boundaries between care and research activities and institutions.[38] From another direction, the availability of commercial, direct-to-consumer genetic testing services allows people to have private access to genomic information that may have reproductive implications for them and their families, representing a third area of growth in genetic screening (alongside mainstream healthcare and biomedical research).[39] Companies that offer such services are building substantial genomic databases, partly with an eye to their commercial value (e.g. to pharmaceutical companies).

1.26 Enthusiasm for the introduction of genetic testing has been tempered by concerns about access to genetic information by others, including employers and insurance companies. This has led to fears of genetic discrimination and a heightening of more general concerns about privacy.[40] Concern has also been registered about the way genetic testing is transforming the nature of clinical encounters and the cognitive and communicative burdens entailed in conveying and managing this sort of information.[41] Despite this, the generation of genome data is undoubtedly increasing and the number of people who have had their genome sequenced is growing, driven by a range of interests, including the public interest in biomedical research.[42] It seems possible that,

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[36] Enabling developments in genome sequencing and associated services are discussed further in Chapter 2 below.

[37] See, generally, Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*, available at: http://nuffieldbioethics.org/project/biological-health-data.

[38] ibid. For example, 'every patient should be a research patient' – these developments have not happened without some difficulty.

[39] A concern expressed at our reproductive genetic fact-finding meeting was the paucity of genetic counselling available with direct-to-consumer genetic testing services.

[40] On genetic screening in employment, see: Information Commissioner's Office (2005) *Employment practices code,* available at https://ico.org.uk/media/for-organisations/documents/1064/the_employment_practices_code.pdf; on genetic discrimination, see: Human Genetics Commission (2011) *The concept of genetic discrimination: a seminar report and reflections and recommendations*, available at: http://webarchive.nationalarchives.gov.uk/20120504100404/http://www.hgc.gov.uk/Client/document.asp?DocId=323&CAtegoryId=10; on genetic testing and insurance, see: HM Government and the Association of British Insurers (2014) *Concordat and moratorium on genetics and insurance,* available at: https://www.gov.uk/government/publications/agreement-extended-on-predictive-genetic-tests-and-insurance.

[41] In a research interview conducted for this project, Lorraine Cowley, Principal Genetics Counsellor at the Institute of Human Genetics at the University of Newcastle, suggested that "recent developments in genetic technology have already changed the role of genetic counsellors. Whole-genome sequencing can produce answers to questions that have not been asked, and there are also problems in interpreting the information that is generated. Scientists produce this information and then genetic counsellors have to relay it to patients, first working out what should be relayed, what's reportable and what people would want to know." Interview with Lorraine Cowley,15 August 2017.

[42] In the UK, for example, the 2017 *Life sciences: industrial strategy* proposals fairly explicitly rests on the foundations of investment in genomic sequencing and exploiting the rich data available through UK public services, most significantly the NHS. It sets out the ambition to create regional Digital Innovation Hubs providing longitudinal primary, secondary and social care and 'community' data (including genomic data) covering between 6 and 25 million citizens initially ("building towards full

all other things being equal, at some stage in the foreseeable future, it will become the norm to have had a personal genome sequence generated.[43] The establishment of such a norm, and the overlaying of a new dimension in the way of thinking about oneself and about others, could significantly affect how people understand relationships between themselves and others at familial and social levels.

Genetic counselling

1.27 Anyone who discovers that they have might have or are carrying a genetic disease should be offered genetic counselling so that they can discuss their health and reproductive options with a genetics professional. The exponential growth in the availability of genetic information, the expansion of genetic testing services into mainstream healthcare, the expectation of increased awareness of the role of genetics as part of background cultural knowledge and the way in which such information might affect individuals and their personal and social relations all suggest that here will be an increasing demand for capacity in clinical genetics and genetic counselling. This has major cost implications and requires suitably trained professionals. There are several possible pathways by which this might be addressed. As part of the current movement towards preventative and precision medicine, which depends on, among other things, knowledge of genetic factors associated with differing reactions to therapeutic agents, this knowledge will inevitably need to be assimilated into the medical mainstream.

1.28 Increasingly sophisticated diagnostic and prescriptive algorithms will be needed to make sense of this data-driven model of medicine. In one vision of the future, the need for human consultation will become marginalised, with clinicians acting more or less as 'customer service agents' for health systems. It is possible to see how this could be a default preference for health service managers motivated by financial concerns. However, the interpersonal and diagnostic skills required by genetic counsellors are not easily acquired.[44] Despite the need for expanded capacity in genetics, the healthcare workforce in many countries including the UK remains generally under-skilled and

population coverage"). This represents a model for the expansion and convergence of information systems that (despite some notable false starts and considerable resistance from privacy campaigners) has long been anticipated. It carries on, for example, in the direction set in the previous 2011 *Strategy for UK life sciences*, available at: https://www.gov.uk/government/publications/uk-life-sciences-strategy. See: Bell J (2017) *Life sciences: industrial strategy – a report to the Government from the life sciences sector*, available at: https://www.gov.uk/government/publications/life-sciences-industrial-strategy.

[43] We will discuss this contention further in Chapter 2. For over a decade, the prospect of universal routine genetic profiling has been under discussion, such as the proposal to sequence all babies at birth for medical purposes (see: Human Genetics Commission and UK National Screening Committee (2005) *Profiling the newborn, a prospective gene technology?*, available at: http://webarchive.nationalarchives.gov.uk/20121102204203/http://www.hgc.gov.uk/Client/document.asp?DocId=154&CAtegoryId=10. This has proved controversial, not least because of the potential collateral uses of large population genomic databases, for example, in biomedical and social research, the design and provision of public services or forensic investigation of crime. See, generally: Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*, available at: http://nuffieldbioethics.org/project/biological-health-data; on forensic uses, see: Nuffield Council on Bioethics (2009) *The forensic use of bioinformation: ethical issues,* available at: http://nuffieldbioethics.org/project/bioinformation and Human Genetics Commission (2009) *Nothing to hide, nothing to fear?*, available at: http://webarchive.nationalarchives.gov.uk/20121102204118/http://www.hgc.gov.uk/Client/document.asp?DocId=226&CAtegoryId=10.

[44] It is possible that developments in artificial intelligence could change this, and this vision has already been suggested, in part, as a way of managing the resource costs in the context of anticipated demands on health services by genomic testing. Direct-to-consumer genetic testing services may be a site of innovation for these services. On requirements for involvement of medical practitioners in feedback of genetic test results, see: Human Genetics Commission (2010) *A common framework of principles for direct-to-consumer genetic testing services,* available at: http://webarchive.nationalarchives.gov.uk/20121102204201/http://www.hgc.gov.uk/Client/document.asp?DocId=280&CAtegoryId=10.

expertise highly concentrated in specialised services.[45] Given the likely growth in genomic testing, with relevance to medical and reproductive decision making, we envisage a need for initiatives on the part of health policy research organisations to explore ways in which genetic counselling capacity, public education and the provision of trustworthy information to the public about genetic conditions could be increased.[46]

The situation facing families with inherited genetic conditions

1.29 Inherited genetic conditions can represent significant burdens to many of those who are affected by them, whether directly or as family members. These burdens include physical, psychological and social impacts and privations as well as financial costs. These factors may be compounded, increasing the risk of co-morbidities, and the economic impact and socio-economic disadvantage of families with certain genetic conditions can be compounded through successive generations.[47] Reducing the burden of non-communicable disease is an objective of public health initiatives that seek to modify adverse factors in the environment or the behaviours of those at risk.[48] Many of these factors, which it is within the scope of public policy to influence, can lead to epigenetic changes that may have more significance in relation to public health than inherited genetic factors.

1.30 Many heritable genetic conditions also represent a financial cost to society via heath systems (mainly funded by taxation in the UK, but by private health insurers in many other countries), although costs associated with serious inherited genetic disease are a relatively small component of the overall cost burden of disease. Health economics is the study of the economics of health systems: the efficiency, effectiveness, value and behaviour in the production and consumption of health and healthcare.[49] A recognition of the costs incurred in meeting the lifetime medical and care needs of people with chronic diseases and disabilities has been taken to support the case for both for the widest availability of elective prenatal screening and for the availability of preimplantation testing for those who have a likelihood of having offspring with certain genetic conditions.[50] This kind of calculation, which evaluates the existence of different people as potential social costs and benefits, is the paradigmatic outlook of the eugenics movements (see Chapter 3 below).[51]

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[45] See: House of Lords Science and Technology Committee (2009) Genomic medicine - 2nd report of session 2008–09, available at: https://publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/107i.pdf. This point was also raised at a fact-finding session. Fact-finding meeting on sequencing, bioinformatics and genomics, 31 July 2017.

[46] Such work being undertaken in the first instance by an independent research organisation or 'think tank', such as the King's Fund or the Nuffield Trust, which has the freedom to think critically and radically.

[47] See, for example: Naylor C, Parsonage M, McDaid D, *et al*. (2012) *Long-term conditions and mental health: the cost of co-morbidities*, available at: https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/long-term-conditions-mental-health-cost-comorbidities-naylor-feb12.pdf.

[48] Genetic factors also play a role in communicable diseases; for example, modifying risk of infection, risk and severity of pathogenicity, etc.

[49] See seminal paper by Arrow KJ (1963) Uncertainty and the welfare economics of medical care *The American Economic Review* **53(5)**: 941-73.

[50] For example, health economists have estimated the average annual cost of care for a person with cystic fibrosis in the UK in 2012 to be equivalent to €48,603. Angelis A, Kanavos P, López-Bastida J, *et al*. (2015) Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom, *BMC Health Services Research* **15**: 428.

[51] This assumes that the person with the condition is replaced by a person who has the same economic impacts in all other respects except for the health costs associated with the condition. In reality, the externalities involved in any change in such a complex system are likely to be hard to account for with any degree of confidence, particularly given that health is strongly linked with the economic productivity of workers (e.g. effects on services, expertise, multiplier effects, transfer of expenditure to co-morbidities, etc.). This may account for some of the notorious difficulty of health service management.

Treatments and care

1.31 Medical treatments for many single gene disorders in many cases are limited to the relief of symptoms and palliative care. A greater range of treatments is often available for cancers, including surgical, chemical, biological and radiation treatments. Where a genetic variant disrupts a particular biological system (e.g. production of blood cells by haematopoietic stem cells in the bone marrow in sickle cell disease), anatomically targeted gene therapy may be possible, with the aim of inserting a more common 'wild-type' version of the variant into cells of the relevant organ or system. These therapies are known as somatic treatments because they notionally intervene in somatic cells (the cells of the body that are not involved in reproduction) as opposed to the reproductive cells that comprise the 'germ line' (which, if altered, can lead to the alteration being passed on to offspring).

1.32 Among the main challenges of gene therapy to date has been delivery of the therapeutic agent to the targeted tissues in the patient at sufficient scale to produce the therapeutic effect, and to do so without unintended adverse consequences and in a way that produces sustained improvement. It is a field to which genome editing, including the use of ZFNs, TALENs and CRISPR-Cas9 systems, has recently given a boost.[52] Treatments with genetically modified cell grafts and transfusions have also been developed for complex diseases; these differ from gene therapy in that correction of the disease-predisposing variant takes place in cells that have been removed from the patient (or a donor) and are then transplanted back.[53] These strategies are all in the early phases of translation to clinical use and there remains uncertainty about which conditions may be tractable to these somatic interventions and which not, and which may prove tractable only to reproductive interventions. Many interest groups sustained either by patients themselves or by pharmaceutical companies offer strong advocacy for the funding and development of new treatments for genetic diseases, including the extension of reproductive options.

The social context

1.33 Although inherited genetic conditions have their roots in underlying biology, the lived experience depends, to an extent, also on contingent environmental (including social) factors. These play a role not only in how different genotypes are expressed for an embodied individual, but also in the way that people are able to respond to their situation (e.g. making use of available treatments or assistive technologies – medicines, wheelchairs, etc.). These conditions include the physical environment and social context (ramps for wheelchairs, supportive family and communities, public services, anti-discrimination legislation), as well as their social and cultural context (genetic conditions may have culturally specific meanings that vary significantly between cultures). They also include individuals' personal attitudes and relationships. For example, the need for assistance, care and treatment may be hard for some people to accept while, for others, they reinforce valued interpersonal bonds.

[52] At the time of writing, approximately 20 clinical trials are registered (although not all of these using CRISPR systems), but this number is rapidly expanding, particularly in China. The genome editing systems, and the prospects and limitations of genome editing gene therapies were discussed in our report, Nuffield Council on Bioethics (2016) *Genome editing: an ethical review,* available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf.

[53] For example, genetically modified T cells (CAR-T cells) were used successfully to treat an infant with acute lymphoblastic leukaemia in 2015 – the first reported therapy relying on genome editing (in this case TALENs).

1.34 The law provides a means of redress for people who experience discrimination as a result of the health effects of a genetic condition. But while under UK equality law disability is a protected characteristic, genetic predisposition to disease, or genetic difference more generally, is not, and many people report experiences of discrimination, stigmatisation and disadvantage linked to their genetic status.[54] This is, in theory, less of a problem in relation to healthcare in the UK, with its tax payer-funded NHS, than in countries in which the costs of private healthcare are largely met from private insurance subscriptions. This has led some countries to introduce genetic non-discrimination legislation in attempts to redress what may be seen as actuarially reasonable but socially unjust penalties for those with pre-existing genetic diagnoses.[55] A similar set of concerns underlies a voluntary agreement (introduced under threat of legislation) between the Government and representatives of the insurance industry in the UK not to use the results of genetic tests in insurance underwriting decisions, and has also been taken up in a recent recommendation of the Council of Europe.[56] Related concerns have been expressed in relation to employers' use of genetic tests as part of medical screening or the exertion of pressure on employees to take genetic tests, although they have not (yet) been realised to such an extent.[57]

1.35 Though the harm of genetic discrimination is often social and economic, until now it has been addressed largely by measures that concern the governance of information (e.g. confidentiality of genome sequence data or genetic test results). Routine use of information technologies and recent developments in data science, however, make such measures increasingly insecure.[58] Since difference from a prevailing norm can open up the possibility of discrimination, it may be that the wish of prospective parents to avoid having a child with a particular condition is influenced not only by their own or the child's immediate interests, but by their anticipation of the child being disadvantaged by a condition that departs from the norm. It is easy to see how having a genetic predisposition

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[54] See: Human Genetics Commission (2011) *The concept of genetic discrimination*, available at: http://webarchive.nationalarchives.gov.uk/20121102221907/http://www.hgc.gov.uk/UploadDocs/DocPub/Document/The%20concept%20of%20genetic%20discrimination%20-%20final.pdf.

[55] See, for example: H.R. 493: Genetic Information Nondiscrimination Act of 2008, 110th Congress 21 May (2008), available at: https://www.gpo.gov/fdsys/pkg/BILLS-110hr493enr/pdf/BILLS-110hr493enr.pdf .

[56] See: HM Government and the Association of British Insurers (2014) *Concordat and moratorium on genetics and insurance*, available at: https://www.gov.uk/government/publications/agreement-extended-on-predictive-genetic-tests-and-insurance; and Recommendation CM/Rec(2016)8 of the Committee of Ministers to the Member States on the processing of personal health-related data for insurance purposes, including data resulting from genetic tests, available at: https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=09000016806b2c5f. Under the *Concordat and moratorium*, insurers agree not to use the results of genetic tests in underwriting decisions except where approved by a committee convened by the Department of Health. Only one test (for Huntingdon's disease for life insurance policies with a value of over £500,000) has been approved for this purpose. The Genetics and Insurance Committee, which, *inter alia*, existed to approve applications from insurers to use genetic test information and received an annual compliance report from the Association of British Insurers, was wound up in 2009 (see Department of Health (2009) *Genetics and Insurance Committee (GAIC)*, available at: http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/ab/Archive/GAIC/index.htm), whereupon some of its functions passed to the Human Genetics Commission, which was itself wound up in 2012. Arrangements were put in place by the Department of Health for the constitution of an *ad hoc* committee to review applications, should this prove necessary.

[57] On genetic screening in employment, see: Information Commissioner's Office (2005) *The employment practices code,* available at: https://ico.org.uk/media/for-organisations/documents/1064/the_employment_practices_code.pdf. This has not been updated for a number of years. (It recommends, for example, that employers "inform the Human Genetics Commission of any proposals to use genetic testing for employment purposes." The Human Genetics Commission was abolished in 2012.)

[58] Lack of openness of algorithms has been a endemic problem for the regulation of insurance underwriting, but it is now becoming a much more widespread source of problems with the extension of automated decision making to more and more areas (such as personal loans, or even the visibility of pages on internet search engines). See: Mills PFR (2016) Ethical reuse of data from health care: data, persons and interests, in *The ethics of biomedical big data*, Floridi L and Mittelstadt B (editors) (Berlin: Springer), at pp 429-44.

to disease might fall into this category. We return to protections against discrimination in Chapter 4.

Reproductive options

1.36 If a person or couple have a significant likelihood of passing on a genetic condition to any offspring they may have, a number of reproductive options are open to them.[59] Which option they pursue is likely to be influenced by their values and beliefs as they relate to the opportunities that are available. Prospective parents may decide to conceive without assistance and not to have testing during pregnancy. They may welcome having a child whether or not the child is affected by the condition, or, though they might prefer to have an unaffected child, they might not consider any other options acceptable. Alternatively, they might opt to remain childless, adopt a child or use a gamete donor, or they might wish to undergo prenatal or preimplantation genetic testing (PGT).

1.37 Prenatal diagnosis (PND) tests for a genetic condition in a fetus. The information it gives can help the pregnant woman prepare for the birth of a child with or without the condition. Alternatively, she might seek termination of an affected pregnancy.[60] Prenatal diagnosis is usually performed by chorionic villus sampling at around 11 weeks after conception (where a small piece of the placenta is removed for genetic testing) or by amniocentesis at around 15 weeks (where a small amount of the fluid surrounding the fetus is removed for genetic testing). Non-invasive prenatal testing (NIPT) or diagnosis (NIPD) is now possible for some conditions.[61] NIPT/D involves analysing 'cell free DNA' from the placenta that is present in the pregnant woman's blood. Placental DNA is very similar to the DNA of the fetus, and there is usually enough cell free DNA in the maternal blood from around nine or ten weeks of pregnancy to get an accurate result. Currently, NIPT/D uses next generation sequencing to determine whether the fetus is likely to have an unusual number of chromosomes (with the aim of estimating the chance that the fetus has a condition such as Down's syndrome) and to diagnose some dominant single gene conditions (such as cystic fibrosis). Whole genome and exome sequencing using NIPT have been carried out in a research setting, but currently this is an expensive and complicated process and is not widely available

1.38 PGT involves testing cells taken from embryos that have been created in a laboratory. Information from the tests is used to decide which embryo (or embryos) should be transferred to the womb.[62] However, in order to have a number of embryos to test, couples have to go through IVF. IVF is a common but non-trivial medical procedure that involves stimulation of the woman's ovaries using hormones and the surgical recovery of the resulting mature eggs. The woman's eggs are then mixed with her male partner's sperm in the laboratory and the formation of the embryos is monitored. A very common

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[59] The usual case would be two parents, one male and one female, although there may be situations in which a woman or man (using the services of a female surrogate), whether alone or in a same-sex relationship, may be at risk of passing on a genetic condition.

[60] In the UK, it is not an offence if a pregnancy is terminated by a medical practitioner at any point up until birth on the condition that, in the opinion of two registered medical practitioners, "there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped." Abortion Act 1967, s.1(1)(d) (as amended).

[61] See Nuffield Council on Bioethics (2017) *Non-invasive prenatal testing: ethical issues*, available at: http://nuffieldbioethics.org/project/non-invasive-prenatal-testing

[62] The term 'preimplantation genetic testing' (PGT) is being promoted by the World Health Organization as a generic term to supersede 'preimplantation genetic diagnosis' (PGD), which was distinguished from 'preimplantation genetic screening' (PGS), which generally meant testing to identify the number of chromosomes present in the embryo, as chromosomal abnormalities (aneuploidies) are known to be a major cause of reproductive failure. PGS is to be referred to, accordingly, as 'preimplantation genetic testing for aneuploidy' (PGT-A). The purpose of PGS is generally related to increasing the chance of having a child through IVF rather than the avoidance of inherited genetic conditions (although embryo selection following PGS offers the opportunity to avoid transferring embryos with non-lethal aneuploidies).

method now employed in clinics is to use intracytoplasmic sperm injection, where a single sperm is injected directly into the cytoplasm of each egg. A few cells are then removed from each resulting embryo, usually from the trophectoderm cell population (the group of cells that would go on to form the placenta in pregnancy) at approximately five to six days after fertilisation. The embryos are usually frozen while the test is carried out on the biopsied cells and the results obtained. A decision can then be made about which embryos, if any, to thaw and place in the woman's womb in the hope of establishing a pregnancy.[63] Many different types of genetic tests have been used in PGT, but next-generation sequencing is becoming the most common technique, by which it may be possible to infer the full genome sequence of every embryo from the biopsied cells.

1.39 In the UK and many other countries, the use of PGT is restricted through regulation and licensed only for the diagnosis of a range of serious genetic conditions or the potential to improve prospects of pregnancy through screening.[64] In 2016 (the last year for which data are available), the Human Fertilisation and Embryology Authority (HFEA) reported that there were 712 cycles of PGT for genetic disease in the UK and 253 live births.[65] It should be noted that PGT does not guarantee a healthy child: a genetic condition can occur as a new event in any pregnancy and undiagnosed conditions cannot be excluded. It should be further noted that the use of IVF to perform PGT increases risks to mother and offspring that are not incurred by prenatal testing.

1.40 Using PGT, the chances of finding any embryo that would not be affected by a single gene condition are three in four for a recessive condition (when both parents are heterozygous), one in two for a dominant condition (when one parent is heterozygous and the other is not a carrier) and three in four for an X-linked disorder (when the mother is heterozygous and the father does not carry the deleterious gene variant). However, in the rare case that a couple carry two disorders, the chances of obtaining an unaffected embryo would diminish. In a very few cases, because of the nature of the genetic endowment of the parents and the mode of inheritance, a given couple may be unable to produce any embryos that do not have a genetic condition they wish to exclude in their offspring.[66] A further complication that may arise from increased knowledge about genetic predisposition to complex conditions such as type 2 diabetes and cancer is that multiple genes may contribute to the risk of disease, but individual genetic contributions are hard to define and may be modified by lifestyle choices. Furthermore, the chances of having a child with selected characteristics are further reduced by the likelihood of any given embryo resulting in a live birth.[67] At the very least, several cycles of IVF might be required. In any of these circumstances, an alternative approach that increases the

[63] There is a possibility that trophectoderm sampling may erroneously suggest aneuploidy; see: Bolton H, Graham SJ, Van der Aa N, *et al*.(2016) Mouse model of chromosome mosaicism reveals lineage-specific depletion of aneuploid cells and normal developmental potential *Nature Communications* **29(7)**: 11165.

[64] The list of conditions for which PGD has been licensed in the UK by the Human Fertilisation and Embryology Authority is available at https://www.hfea.gov.uk/pgd-conditions/; further conditions may be added to this list by application to the Authority.

[65] The data and information in the accompanying report (Human Fertilisation and Embryology Authority (2018) *Fertility treatment 2014–2016: trends and figures*, available at: https://www.hfea.gov.uk/media/2563/hfea-fertility-trends-and-figures-2017-v2.pdf) do not allow certainty about how many babies were born from treatments that took place in any given year.

[66] These are very rare, but very significant where they exist. A known example is autosomal recessive non-syndromic sensorineural deafness. See also Chapter 2, where we discuss possible use cases.

[67] The latest Human Fertilisation and Embryology Authority data available for PGD cycles show an overall live birth rate per embryo of 33%, which compares favourably to IVF overall, probably as a result of the downward trend, identified in the report, in age of women who opt for PGD; see: Human Fertilisation and Embryology Authority (2018) *Fertility treatment 2014–2016: trends and figures*, available at: https://www.hfea.gov.uk/media/2563/hfea-fertility-trends-and-figures-2017-v2.pdf. There is no finer detail of the case mix, but it may be assumed that the majority are autosomal recessive conditions and chromosomal rearrangements.

chances of having a child with the preferred genetic features would have obvious advantages.

1.41 Two potential approaches could satisfy the desire for a child with a biological link to both parents where other routes to parenthood are either unavailable or unacceptable. The first would be dramatically to increase the number of embryos available in order to increase the chances of finding an embryo with the desired genetic variants by PGT.[68] The second would be to modify the embryos that are available so that they carry the desired genetic variant or variants. The limiting constraint in the first approach is the availability of mature eggs (sperm are sufficiently numerous and can usually be obtained without surgical intervention).[69] Some promising research has been carried out in mice into the derivation of functional gametes (both sperm and eggs) from stem cells, but it is unclear whether the extrapolation of these approaches to humans is achievable in the foreseeable future, owing to differences in gametogenesis between mice and humans.[70] The second approach implies the use of genome editing techniques that could be sufficiently refined for use in early embryos.[71] Unlike PGT, the genome editing approach is not limited to the range of genetic permutations available from the parents (permutations that, given sufficient time and reproductive health, might have come about through unassisted conception), but offers the prospect of introducing variation that is not present in their immediate genetic lineage and, conceivably, has not yet been found in any other person.

Framing the challenge to be addressed

1.42 In concluding this chapter, and to prepare the ground for the ethical examination that will follow in Chapter 3, we turn to the question of what is at stake in the prospective use of interventions to secure the birth of a child in a way that excludes or includes certain genetic characteristics. In other words, we are interested in how we 'frame' questions about genome editing in human reproduction.[72] How we frame our questions encodes social phenomena in particular ways. Interrogating the framing of social phenomena helps to reveal what people think they are talking about when they engage in discussion of a particular subject, and therefore how meanings are assigned, asserted and circumscribed and how misunderstandings arise. In our 2016 report, *Genome editing: an ethical review*, we said:

> "*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;*

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[68] Finding a suitable embryo will still depend on chance and on segregation of the various alleles associated with disorders. If two genes are closely linked, it may never be possible to separate them. In any case, the more characteristics being screened for, the less likely it is to find an embryo with none of them.

[69] Advances in egg freezing (up to a point) and *in vitro* growth and maturation of oocytes, which offers the prospect of generating large numbers of useable oocytes from the ovarian primordial follicle pool, could help address this to an extent; see: McLaughlin M, Albertini DF, Wallace EHB, *et al.* (2018) Metaphase II oocytes from human unilaminar follicles grown in a multi-step culture system *MHR: Basic Science of Reproductive Medicine* **24(3)**: 135–42.

[70] See: Fayomi AP and Orwig KE (2018) Spermatogonial stem cells and spermatogenesis in mice, monkeys and men *Stem Cell Research* **29**: 207–14. Engineered egg cells form the basis of a future of 'easy PGD' imagined by medical lawyer and bioethicist Hank Greely. He makes the point that easy PGD would be "in effect, 'free' to the health care system," even before counting the costs of higher risks of later-onset and complex diseases that might be avoided; see: Greely H (2016) *The end of sex and the future of human reproduction* (Cambridge, MA: Harvard University Press).

[71] Earlier, untargeted approaches to genetic engineering or gene therapy have not reached the level of refinement that would make them suitable for genome modification in early embryos.

[72] Framing, in this sense, is related to, but different from, various discursive phenomena that might influence attitudes to uses of genome editing (i.e. it is not generally about *bias*, the preferential presentation of one possible outcome (or a range of possible outcomes) over another (or others) but about *meaning*). The question of 'frame effects' influencing behaviour was researched in Weisberg SM, Badgio D, and Chatterjee A (2017) A CRISPR new world: attitudes in the public toward innovations in human genetic modification *Frontiers in Public Health* **5(117)**: 1-9. Their findings suggest that presenting information about genetic modification as contrasting vignettes using one of five 'framing' metaphors (genetic editing, engineering, hacking, modification or surgery) made little difference to public attitudes.

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."

Necessary and sufficient reasons

1.43 Particularly around matters of procreation and health, people's motives and aims may be complex, inconsistent, fluctuating and emotionally charged. They are also often obscure, perhaps even to the people themselves, and furthermore, practically impossible for others to verify. This is no doubt all the more true in cases in which there is a known, non-negligible prospect of having a child with a genetic condition. We can, however, try to arrive at a clearer description of this general situation by asking what must be the case for heritable genome editing interventions to be a possible and then perhaps a preferred course of action. The hypothetical use of heritable genome editing interventions is often presented as something like 'helping people to avoid having a child with a genetic condition'. This description is, however, rather misleading. What people want is not, for example, to avoid having a child (which could be accomplished relatively simply by various means of contraception). Parsing this more carefully, we understand that:

- they want to *have a child, and*
- they want the child they have to be *genetically related to them* (otherwise the pre-established likelihood of the child having the genetic condition in question disappears or, at least, changes), *and*
- they want the child they have *not to have a specified condition* that there is a supposed likelihood that that child will have (which means, at the genetic level, they want the child to have one specified genetic variant rather than another), *and/or*
- they want the child they have *to have a specified characteristic* that there is a supposed likelihood that that child will not have (or, again, they want the child to have one specified genetic variant rather than another).

1.44 This means that the prior and necessary condition is not wanting *to avoid* an outcome (which requires very little agency), but wanting *to achieve* an outcome (having a child), albeit subject to certain conditions. This requires some sort of more deliberate agency. Having children is not something that happens to people, but something that they cause to happen as agents (even if it is sometimes an unintended consequence of action motivated by other desires). In this case, the outcome is very specific and deliberate: the prospective parents want children, but they do not want *those* children; they want *these* children instead. While it is no doubt the case that the *motivation* for having children is rooted in deep and complex desires, the choice to use reproductive genetic technologies as a means is necessarily very deliberate.

1.45 Before they decide to use reproductive genetic technologies, prospective parents have to know something about the likelihood of having children with certain genetic characteristics for this to become a salient question. They might know this as a result of

a previous affected pregnancy or child or the identification of the genetic condition among their biological relatives through preconception genetic testing or even speculative genome sequencing. Their choice should also be informed by knowledge about the condition and how it is inherited. They will know also about the range of alternative approaches they could take and something about the range and likelihood of the different outcomes in which each of these might result. Particularly with novel approaches, such as heritable genome editing interventions, there might be significant uncertainty about both the range and likelihood of outcomes.[73] This knowledge and its limitations put them in a distinctive 'epistemic position' – a position of knowing or having reason to believe certain things – from which they must decide on a course of action from among those that are available. As we discussed above, the context of genetic knowledge and technology confronts prospective parents with new opportunities, but also new dimensions of responsibility for acting or not acting.[74] It is our conjecture that the trend of increasing genomic information (both about the genomic factors that contribute to observable traits in general and about the genetic endowments of particular individuals), combined with the development of new technologies and treatments, will only make complex reproductive decisions more common.

1.46 There are, in the UK as in many other societies, many possible routes to parenthood that would not entail the likelihood of having a child with a genetic condition identified in the prospective parent(s).[75] These generally require the assistance of a third party to a greater or lesser extent – social assistance in the case of adoption, social and/or medical assistance in the case of gamete donation, etc.[76] They may also require a background of moral approval on the part of broader society – in each case, further morally relevant considerations are engaged. In the case of selective termination of pregnancy or preimplantation selection among embryos, further morally relevant considerations include that the condition to be avoided is one that it is, in the circumstances, regarded as acceptable to want to avoid.[77] This is a highly contested area and a large margin is conventionally allowed to accommodate the private views and values of people seeking treatment.[78]

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[73] There is substantial literature on the psychological, sociological, economic and public policy approaches to risk and uncertainty. The basic distinction is that, with risk, probabilities can be assigned to a known range of different outcomes; where the range of outcomes cannot be known and therefore the likelihood of any outcome cannot be predicted with any confidence, uncertainty is present. Radically different strategies may be appropriate when approaching risk and uncertainty.

[74] See the discussion of 'responsibilisation' in relation to developing genetic knowledge. Of course, it is misleading to suggest that all – or even most – of the responsibility really falls on parents, or perhaps it does so only at the very last moment, by which time their degrees of freedom are already set. Although consent to treatment is rightly a necessary condition of treatment being provided, the idea that informed consent, promulgated as a cornerstone of medical ethics, gives individuals control over their options is at most a half-truth. Their effective consent is only the final point up to which the exercise of many other forms of agency have led.

[75] For most of human history, these options would have been relatively limited, probably to not having children or not having children who are directly biologically related to the prospective parents. Adoption and surrogacy have long been practised (under a variety of rubrics and customs) in many cultures, and gamete donation (overt or covert) may have a longer history than is generally supposed; conversely, the practice of infanticide has been extirpated from most known societies on moral grounds. Reproductive technologies requiring surgical and laboratory procedures (egg/embryo donation, prenatal diagnosis and the lawful medical/surgical termination of pregnancy and preimplantation testing) only appeared in the twentieth century.

[76] 'Generally' because all lawful ones, which involve acquisition of parental responsibility, involve professionals, although it is conceivable that people may bring up a child of relatives, for example, without formal transfer of legal responsibility.

[77] The HFEA maintains a list of conditions for which licences for PGD have been approved, in which the nature of the condition to be avoided is a consideration. This does not appear to be a criterion for gamete donation – people may be accepted into gamete donation treatment for a wide variety of reasons and are not necessarily denied treatment because a condition that they and their partner together might pass on is regarded as normatively insufficient to justify the treatment.

[78] The history of abortion and PGD provision shows how the interpretation of the criteria of 'significant risk' and 'serious condition' has tended from normative to subjective (or situated) over time.

1.47 Of the routes to parenthood that may be available, however, only some involve the creation of a child who is directly genetically related to both their parents.[79] The preference for options that secure direct genetic relatedness between parents and children reveals how this is valued by individuals (by choosing these options over arguably less burdensome options that do not secure genetic relatedness) and the value placed on making these options available by society.[80] (We will examine this in more detail in Chapter 3.) In practice, the choice may be affected by factors other than the value placed on different options, however. Access to some reproductive options may be limited. For example, opportunities for adoption, particularly of babies and young infants, do not meet demand, the process is lengthy and demanding and it creates a situation with additional dimensions of psychosocial complexity.[81] Donated gametes have been in short supply in the UK in the past, although there is evidence that this is less of a problem at present and may get easier in the future.[82] While demand for assisted reproductive treatments may, in many cases, be driven by a preference on the part of prospective parents to use their own gametes, in some cases it might be driven by the limited availability of what they would consider to be acceptable alternatives.

Reproductive and therapeutic perspectives

1.48 It follows from what we have said above that preimplantation genetic technologies offer ways of satisfying the reproductive goals of prospective parents, which are arrived at in the knowledge of certain biological constraints (the likelihood of having an affected child) and are subject to certain voluntary conditions (the condition that the child should be biologically related to the parents). This suggests that they are more complex and differ in important respects from straightforwardly 'therapeutic' treatments, the object of which would be to restore to health or alleviate the suffering of people who are affected by disorders.

1.49 If an intervention cannot be described as straightforwardly therapeutic, it equally cannot be described as straightforwardly preventative, and for the same reason, its primary referent is not an actual person but a possible person. To describe it as prevention would be to ignore the agency involved in reproduction. To speak of a heritable genome editing intervention as prevention makes more sense, however, within the conceptual frame of public health, where the intervention becomes a question not of individual well-being, but of the health of a population. (We discuss this in Chapter 3 under the rubric of 'eugenics', since it raises questions about the kinds of people that are in the population rather than the conditions by which the people in the population are contingently affected.)

1.50 Understanding the significant extent to which genome editing is concerned with reproductive goals may have significant consequences for the orientation of our inquiry.[83]

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[79] Intra-family gamete donation (e.g. egg donation between sisters) is favoured in some cases, which maintains a close – but not direct – biological link (although there may also be other reasons for this practice, such as donor suitability and gamete availability).

[80] We will consider the moral significance of this preference in Chapter 3.

[81] The increasing availability of lawful, safe abortion in many societies in the last half-century has meant fewer babies have been available for adoption than in previous generations.

[82] See: Human Fertilisation and Embryology Authority (2018) *Fertility treatment 2014–2016: trends and figures*, available at: https://www.hfea.gov.uk/media/2563/hfea-fertility-trends-and-figures-2017-v2.pdf. It should be emphasised that it is nevertheless not the general availability of donors *per se*, but the availability of donors who are regarded a suitable for particular patients that matters in each case.

[83] This observation is made in reports on mitochondrial donation and on genome editing by working groups convened by the US National Academies of Sciences, Engineering, and Medicine, although in both their advice is ultimately cast in a 'medical' frame. See: The National Academies of Sciences, Engineering, and Medicine (2016) *Mitochondrial replacement techniques:*

The most obvious consequence is that we must approach the question of the ethical permissibility of using novel treatments, such as heritable genome editing interventions, not simply by weighing the consequences for a putative future child of having or not having a given condition, but also, and firstly, by understanding the implications for parents of having or not having access to a certain treatment. This does not mean that the possible consequences for the future child will be irrelevant with regard to the question of whether to provide access to those treatments (or to limit it). It does mean, however, that we must consider this in the context of the value placed on prospective parents' reproductive aims and the acceptability of certain kinds of reproductive goal in a concrete socio-technical context – the context of the knowledge, assistance and support that could be made available to them.

1.51 Talk of assisted reproductive technologies as 'therapeutic' is nevertheless a way of speaking that is often threaded through discussions about them. After all, infertility is regarded as a disorder that merits clinical treatment.[84] Though the prospective parents may not be clinically infertile, the prospective parents are clearly not in the same position as people who do not know that, if they have a child, there is a significant likelihood that this child would be affected by a condition they wish to avoid.[85] Whether their childlessness is the result of a biological impairment or the decision not to have a child with a given condition, the personal emotional impact may be equally profound. From the point of view of prevailing norms of parenthood, they may be said to be at a disadvantage. At the very least, it would seem inconsistent if the situation of someone in this position were not to engage compassion in the same way that infertility engages compassion. Whether infertility or certain kinds of genetic condition are regarded within the range of normal variation or as requiring special consideration from others, they can affect individuals in profound and personal ways. Assisted conception that allows people to have the kind of children they want could perhaps, therefore, be said to be therapy in the sense that it provides a way of redressing what is normatively perceived as a reproductive disadvantage.

Conclusion

1.52 In this chapter, we have considered the situation facing people with inherited genetic conditions in the context of continuing developments in genomic knowledge and reached two conceptual conclusions that will be of importance for our inquiry.

1.53 The first conclusion arises from the epistemic shift that has been brought about by the increasing background knowledge of genetic differences that genomics research reveals. This further reveals the inadequacy of the simple distinction between health and disease as a way to think about different forms of embodiment and complicates understanding of the responsibilities that such knowledge entails. It highlights how

ethical, social, and policy considerations, available at: https://www.nap.edu/catalog/21871/mitochondrial-replacement-techniques-ethical-social-and-policy-considerations, and National Academies of Sciences, Engineering, and Medicine (2017) Human Genome Editing: Science, Ethics, and Governance, available at: https://doi.org/10.17226/24623.

[84] Some IVF is even funded and provided via the NHS in the UK. The NHS England commissioning guidance for PGD nevertheless states clearly that: "The aim of a PGD service is to allow couples at significant risk of having a child with a genetic disorder, to have a child that is genetically related to them and at very low risk of being affected." It furthermore presents PGD as an alternative to PND and termination of pregnancy because, "For some people, termination of pregnancy is either unacceptable or less preferable." See: NHS England (2014) Clinical commissioning policy: pre-implantation genetic diagnosis (PGD) (reference: E01/P/a), available at: https://www.england.nhs.uk/wp-content/uploads/2014/04/e01-med-gen-0414.pdf.

[85] A number of genetic conditions are, however, associated with reduced fertility or infertility; see: Zorrilla M and Yatsenko AN (2013) Genetics of infertility – current status of the field *Current Genetic Medicine Reports* **1(4)**.

normative dichotomies that often appear in discussions about the moral dimensions of genome editing in reproductive contexts can be unhelpful and possibly misleading.

1.54 The second conclusion concerns how we frame questions about genomic interventions in reproduction. Our discussion suggests that what is at stake in such questions is both distinct from and more complex than what is at stake in questions of treating existing people affected by clinically diagnosed conditions, even if they are similarly rooted in compassion and respect for others. This conceptual difference explains our decision to deal, in the present report, with genome editing in the context of human reproduction as distinct from other human applications (e.g. in somatic gene therapy), rather than treating them together.

1.55 In closing this chapter, we wish to sound a note of caution. The impetus for this report comes from the prospect of the emergence of heritable genome editing technologies, and much of the present chapter has been concerned with the implications of different genomic factors on the health of human beings to the extent that they might be the subject of people's aims and goals. Research continues to identify genomic factors associated with ostensible conditions, but these genetic factors are often far from determining and they may be highly complex. We will therefore have to consider cases in which the preference for including or excluding a given trait may be very strong, but its expression highly uncertain and subject to many other influences, controls and mitigations. It is to the theoretical potential of genomic technologies and practical conditions for their development that we turn in the next chapter.

Chapter 2

The horizon

Chapter 2 – The horizon

Chapter overview

This chapter 2 expands the focus from individuals confronting personal decisions in the light of certain kinds of background knowledge and specific information (discussed in Chapter 1) to the way in which the technologies by which they are surrounded bring them into the position where they can express their moral agency in different ways. The chapter falls into two halves, the first dealing with scientific and technological context and the second dealing with the non-technical (social) context.

The chapter first describes recent development of genome editing systems, in particular systems based on CRISPR-Cas9, and its use in human embryo research. It identifies a number of possible strategies that might make use of genome editing to influence or secure inherited characteristics in offspring. These include modifying gametes prior to fertilisation and modifying early embryos *in vitro*. It describes how further developments in genomics might expand the repertoire of potential uses for these techniques.

The second part of the chapter explores the conditions and dynamics according to which innovation, diffusion and further expansion of the use of genome editing technologies might take place. While it is not possible to predict the course of development, the chapter identifies a number of potential 'use cases' for heritable genome editing interventions. Among them are very rare cases of inherited genetic conditions where the chances of having a genetically related child without the condition are slight, and cases where predisposition to complex diseases cannot be reduced significantly by selective techniques. The chapter then looks at the drivers and conditions that could lead to a diffusion of heritable genome editing for closely and more remotely related reasons.

The chapter then draws attention to the conceptual, institutional, regulatory and economic factors that may determine whether and how genome editing technology enters into use, and the social and moral norms that will affect its acceptability. It notes that technology and the social environment in which it develops can influence each other reciprocally, such that the use of technology may secure, embed or transform the conditions by which it is received in that social context. Reflecting on these processes helps to identify sites and opportunities for more constructive governance, prioritisation and control, including the role that moral judgement might play.

Introduction

2.1 The discussion of genome editing has, for the most part, been focused on research and on innovation: on the techniques being developed in research laboratories and on the conditions under which we might make the first move from the laboratory to the clinic (or the factory, or the field). This step is an important one, but in many ways it is only a first step. If a technique is used once, and perceived to be successful, it is likely that this first step will not be the last. The greater the perceived success, the more users it is likely to attract. From here, use of the technique can be expected to increase and its impact spread. If the first step is successful, the questions then arise of how widely use of the technique will spread, what will encourage or restrict its diffusion, what incumbent approaches it will displace and in what other circumstances, beyond those marked out for the first use, it may be used. In considering these questions, we will have to understand how practice, skills and capacities, management pathways, funding streams, professional knowledge, etc., may adapt and reform around the technology in use. This

chapter is concerned with these sorts of questions: thinking about genome editing *as a prospective biomedical technology* rather than as an isolated innovation decision.

2.2 It is, of course, possible that the first step into clinical use may never happen for heritable genome editing interventions. At present, 'genome editing' describes a suite of biological techniques that are predominantly used in research. These are only beginning to be incorporated into a number of emerging biotechnologies and biomedical technologies, as these take shape in a variety of fields.[86] The course of these technological developments will depend on a variety of factors, among them the development and translation of multiple distinct forms of knowledge and technical skill (e.g. the identification and characterisation of genome targets), other converging and enabling technologies (e.g. techniques for delivering the editing machinery effectively into the target cells) and securing the conditions that cause the modified cells to function in the organism in the way intended (and, if they do, in the absence of collateral, pleiotropic effects).[87] It will also depend on a number of organisational, social, political and economic conditions. Thus considered, the emergence of genome editing technologies appears less like the conclusion of a series of logical steps than the resolution of a large number of complex forces, which potentially confound expectations about what are the most likely points of innovation and the most significant sites of agency, influence and control.

2.3 Most importantly for our purposes, the development of genome editing technologies confronts moral objections that may result in effective limitations on practice (e.g. if they are enshrined in laws, professional standards, codes of conduct, social norms or the individual consciences of practitioners).[88] We will need to examine, therefore, how moral agency may come to influence or constrain practice and also when it might not. Furthermore, where agency and moral influence do hold sway, we will need to understand not only how the development of technology may be made to conform with moral norms, but also, in turn, how familiarity with technology can affect those norms. Ultimately, however, we must acknowledge that, even though it may have been subjected to a great deal of examination and supported by a convincing moral case, genome editing as a way of influencing inherited characteristics could fail owing to intractable technical difficulties or perhaps as the result of a better alternative being adopted instead.[89]

2.4 Science and technology are developing rapidly in this field. In a report that it is hoped will have relevance to governance debates and decisions beyond the near term, we should be cautious about predicting the precise form of the technology that we might be trying to govern in 5–15 years' time. Nevertheless, to provide some context for our discussion, we will delineate the broad contours of prospective technological advances as they appear at present, conscious that they may take unexpected turns.

2.5 In this chapter, we will be guided by two questions in particular: firstly, in what ways might genome editing be implicated in emerging biomedical technologies that enable the influencing of inherited characteristics? Secondly, what norms, interests, power relations

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[86] We surveyed a number of these fields of application in an earlier report; see: Nuffield Council on Bioethics (2016) *Genome editing: an ethical review*, available at: http://nuffieldbioethics.org/project/genome-editing.

[87] In a 2012 report, we characterised a biotechnology as a productive assemblage of knowledges, practices, products and applications; see: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good,* available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf.

[88] Of course, moral objections might be overcome by other considerations: see: Baylis F and Robert JS (2004) The inevitability of genetic enhancement technologies *Bioethics* **18***:* 1–26.

[89] This could happen, for example, if demonstrably effective perinatal or later somatic cell therapies or interventions became established.

and societal consequences are brought into play when we consider the prospect of genome editing technologies in use in society? Having surveyed this horizon, in the next chapter, we consider whether heritable genome editing interventions can be morally permissible and, if so, what principles should guide their use.

The potential of genome editing

Genome editing systems

2.6 In cases in which it is possible to know, with sufficient confidence, the biological functions of a given genome sequence and the consequences for the organism of different specific variations in that sequence, it may be possible to 'edit' that sequence to achieve a desired outcome in the organism (or to make such an outcome more likely). The basic principles and development of genome editing techniques were described in our earlier report, *Genome editing: an ethical review*.[90] At that time, the focus was primarily on CRISPR-based systems that had risen rapidly to prominence following the publication of the underlying biological mechanism in 2012.[91] However, we have kept the definition of 'genome editing' broad so as to accommodate other possible approaches.[92] These include systems that predate the development of CRISPR-based systems (e.g. zinc finger nucleases and TALENs) and have been used in the clinic following lead periods of translational research.[93] They may also include further and as yet unimagined platforms.

Diversification and refinement

2.7 Genome editing systems have two important components: one to guide the editing machinery to the site in the genome where the modification is to be made and the other to effect the modification. The genome is encoded as a series of chemical bases that are arranged along the length of the DNA molecule, a long molecule that has the structure

[90] Nuffield Council on Bioethics (2016) *Genome editing: an ethical review*, available at: http://nuffieldbioethics.org/project/genome-editing.

[91] The initial work for which the collaboration between Jennifer Doudna and Emanuelle Charpentier became renowned was published in 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. Doudna and Charpentier, and also Feng Zhang at the Broad Institute, became the names most closely associated with CRISPR-Cas9 (partly owing to their battle over intellectual property in the US and Europe), with the parallel work of Virginijus Siksnys also recognised along with that of Doudna and Charpentier with their joint award of the 2018 Kavli Prize in Nanoscience. As so often in scientific research, however, the lionisation of these senior researchers should be seen within the context of prior and subsequent work. The underlying mechanism of CRISPR was, for example, described in Archaea by Francisco Mojica in 1993, who is later said to have coined the term 'CRISPR' in correspondence with a colleague (see: Mojica FJM, Juez G., and Rodrıguez-Valera F (1993) Transcription at different salinities of *Haloferax mediterranei* sequences adjacent to partially modified *Pst*I sites, *Molecular Microbiology* **9(3)**: 613–21; Davies K and Mojica F (2018) Crazy about CRISPR: an interview with Francisco Mojica *The CRISPR Journal* **1**: 5) and earlier in bacteria by Ishino and colleagues (see: Ishino Y, Shinagawa H, Makino K, *et al.* (1987) Nucleotide sequence of the *iap* gene, responsible for alkaline phosphatase isozyme conversion in *Escherichia coli* and identification of the gene product *Journal of Bacteriology* **169**: 5429–33), while the conjunction of CRISPR and CRISPR associate nucleases (CRISPR-Cas) was identified as a proto-immune system from 2007 (see: Barrangou R, Fremaux C, Deveau H, *et al*. (2007) CRISPR provides acquired resistance against viruses in prokaryotes, *Science* **315(5819)**: 1709–12).

[92] We have characterised 'genome editing' as "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." We noted that such targeted alterations "may be accomplished in different ways, including through the use of new and emerging techniques such as the CRISPR-Cas9 system… In the future, they may be accomplished in ways that have not yet been described or even envisaged" and "genome editing also includes making alterations to non-coding regions of genomes and to epigenomes" (Nuffield Council on Bioethics (2016) *Genome editing: an ethical review*, available at: http://nuffieldbioethics.org/project/genome-editing).

[93] The TALENs system was used to modify cells that were transfused to effect a cure in the case of an infant girl affected by refractory relapsed acute lymphoblastic leukaemia in the UK in 2015 (see: 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).

of a helix with two entwined strands.[94] The CRISPR-Cas9 system operates by causing a double-strand break (DSB) in the DNA molecule at the chosen location.[95] This process is depicted in the 'Genome editing mechanisms' diagram below ('Double-strand break').

2.8 DSBs, which can occur naturally, are potentially lethal for cells. Cells have evolved two principal DNA repair pathways that can be co-opted to repair the break caused by the Cas9. In one pathway, non-homologous end-joining (NHEJ), DNA bases are typically introduced or deleted at the cleavage site in an uncontrolled manner as a result of the repair process. (These uncontrolled insertions and deletions are known as 'indels'.) In the other, homology-directed repair (HDR), an additional DNA molecule is used as a repair template. These processes are depicted in the 'Genome editing mechanisms' diagram below ('DNA repair in the cell by different pathways').

2.9 Whereas NHEJ entails a degree of randomness that cannot be voluntarily controlled, HDR permits the introduction or deletion of prescribed sequences at or near the site of the DSB, according to the template used. The usefulness of systems that harness the NHEJ pathway consists primarily in disrupting gene function (by the random addition or deletion of bases), which has its main use in biological research to identify the role played by specific sequences, although it may be used clinically in certain cases, such as to promote exon skipping in order to neutralise the effect of disease-causing variants. The HDR pathway, however, because it allows predetermined changes to be made to the DNA sequence, is thought to have potential utility in clinical applications.

2.10 Since the advent of CRISPR-Cas9, a Cas9-based toolkit has been expanded significantly.[96] As well as modifying the genome itself, variations on the system can also be used to modify the epigenome – a set of chemical compounds attached to the DNA molecule or to proteins (histone variants) that coat the DNA (in chromatin) – to control how the genome is expressed. Epigenome editors do not alter the DNA sequence itself, but rather the activity of a given sequence. Unlike the genome, which is inherited from the parents but remains largely static for an individual organism, the epigenome can be modified by environmental interactions. Variations of epigenome editing have been developed, typically based on a modified Cas9 such as dCas9 ('dead' Cas9) that lacks DNA-cutting activity but to which the appropriate epigenome-altering activity has been linked. This activity change is reversible and may only be short-lived, but some epigenetic characteristics are extremely stable in genomes, and in some but not all cases these modifications can be passed on to the organism's descendants. This process is depicted in the 'Genome editing mechanisms' diagram below ('Epigenome editing').

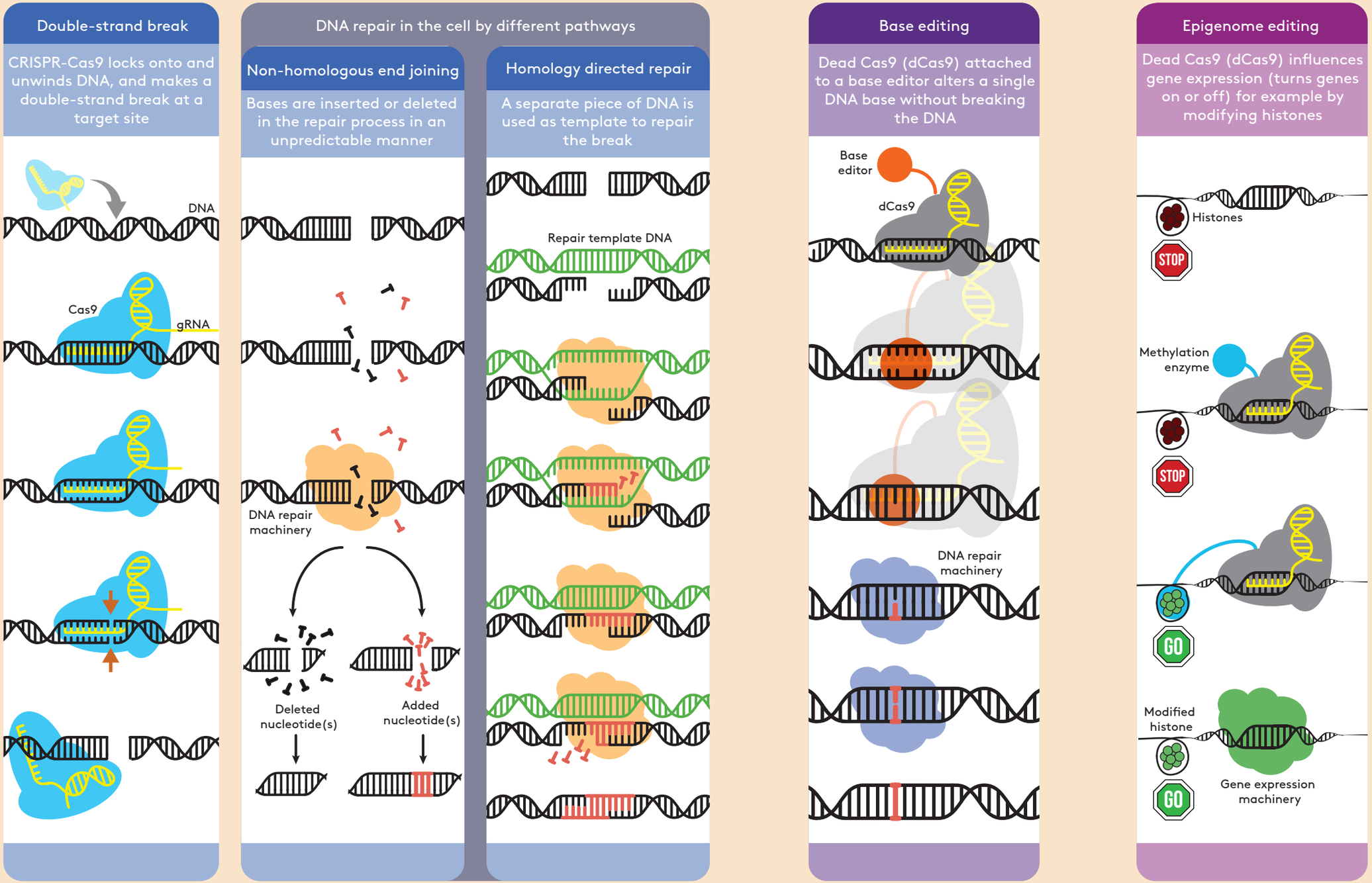
2.11 The dCas9 framework has also been adapted to 'base editing', in which a single specific base, the fundamental element of the genome sequence, is converted into a different base. This has great therapeutic promise as a large proportion of Mendelian disorders identified in humans are due to single-base substitutions. Like the dCas9-based epigenome editing systems, base editing is programmable and does not require a repair

[94] Crick FC and Watson JD (1953) Molecular structure of nucleic acids, a structure for deoxyribose nucleic acid *Nature* **171(4356)**: 737–8.

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

[96] For example, new Cas9 variants have been found or developed that have a reduced target criterion, such as xCas9, which can recognise a broad range of protospacer adjacent motif (PAM) sequences; see: Hu JH, Miller SM, Geurts MH, *et al*. (2018) Evolved Cas9 variants with broad PAM compatibility and high DNA specificity *Nature* **556(7699)**: 57–63.

Genome editing mechanisms



template or DSBs, so any risk associated with 'indels' is avoided. Base editing relies on DNA mismatch repair mechanisms, which enable the cell to recognise and correct errors that can arise during DNA replication and recombination or as a result of DNA damage. The technique has been developed to allow a number of potentially therapeutic pairwise base transitions within the genome, changing a C into a T (or, strictly, uracil) or an A into a G (or, strictly, inosine).[97] The changes produce base pair mismatches that are efficiently resolved by cellular repair pathways.[98] Base editors can now change adjacent bases simultaneously.[99] This process is depicted in the 'Genome editing mechanisms' diagram below ('Base editing').

Use in human embryos

2.12 When we published our previous report in September 2016, only two papers in the scientific literature had reported the use of genome editing techniques in human embryos. Both used tripronuclear (3PN) embryos (embryos with three rather than two pronuclei) and both were from China.[100] Since then, research has appeared using genome editing in ostensibly healthy embryos to correct a variant of the *HBB* gene, which encodes β-globin (the variant associated with the blood disease, beta-thalassaemia) and to modify a variant of the *G6PD* locus (a variant associated with the disease favism, common among the Chinese Han population).[101] There has also been further research in animal models, including primates (e.g. editing *HBB* genes in rhesus monkeys).[102] Base editing has been used by a team in China to modify *HBB* mutations in cloned embryos generated by transferring nuclei of cultured cells from an affected (homozygous) male β-thalassaemia patient and eggs donated by patients undergoing *in vitro* fertilisation (IVF) treatment.[103] What is perhaps significant about this research is not the number of papers (that there are few or that there are any at all), but the fact that research to correct mutations in human embryos that are potentially capable of normal development is now established in the literature.[104]

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[97] 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; Shimatani Z, Kashojiya S, Takayama M, *et al.* (2017) Targeted base editing in rice and tomato using a CRISPR-Cas9 cytidine deaminase fusion *Nature Biotechnology* **35(5)**:441–3; Gaudelli NM, Komor AC, Rees HA, *et al*. (2017) Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage *Nature* **551(7681)**: 464–71; Komor AC, Badran AH, and Liu DR (2018) Editing the genome without double-stranded DNA breaks *ACS Chemical Biology* **13(2)**: 383–8.

[98] Eid A, Alshareef S, and Mahfouz MM (2018) CRISPR base editors: genome editing without double-stranded breaks *Biochemical Journal* **475(11)**: 1955–64.

[99] Base editors can now change adjacent bases simultaneously; Ryu S-K, Koo T, Kim K, *et al*. (2018) Adenine base editing in mouse embryos and an adult mouse model of Duchenne muscular dystrophy *Nature Biotechnology* **36(6)**: 536–9.

[100] 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. It was assumed that the researchers used 3PN embryos in order to counter some potential ethical objections to the research, since embryos with three pronuclei were not thought to be capable of development and could not be used in treatment.

[101] See: Tang L, Zeng Y, Du H *et al*. (2017) CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein *Molecular Genetics and Genomics* **292(3):** 525–33.

[102] Midic U, Hung P, Vincent KA, *et al*. (2017) Quantitative assessment of timing, efficiency, specificity, and genetic mosaicism of CRISPR/Cas9 mediated gene editing of hemoglobin beta gene in rhesus monkey embryos *Human Molecular Genetics* **26(14)**: 2678–89.

[103] Liang P, Ding C, Sun H, *et al.* (2017) Correction of β-thalassemia mutant by base editor in human embryos *Protein & Cell* **8 (11)**: 811–22. The donated eggs were immature at the point of recovery and therefore unsuitable for use in treatment, but were subsequently matured *in vitro* to enable them to be used in research.

[104] At the time of writing, the first licence for research involving genome editing had been issued by the Human Fertilisation and Embryology Authority (HFEA) in February 2016. One of the salient arguments that eased acceptance of the research was that the study was basic research aimed at improving understanding of early pregnancy loss and not a potential therapeutic target. Findings from this research have been published in Fogarty NM, McCarthy A, Snijders KE, *et al.* (2017) Genome editing reveals a role for OCT4 in human embryogenesis *Nature* **550(764)**: 67–73.

2.13 It is important to recognise the uncertainty that continues to exist about the technical efficacy of genome editing in human embryos. First, it must be established whether CRISPR-Cas9 systems faithfully cleave their intended genomic target without uncontrolled cutting of other sequences ('off-target events') in ways that would make them unsafe for clinical use.[105] Second, it is uncertain whether the HDR pathway can be recruited to produce the desired genome change at sufficiently high frequencies for effective clinical use or, if so, how. Work on the mouse suggests that the cells of two-cell embryos efficiently support HDR with up to 95 per cent successful targeting.[106] Doubts pertaining to the first concern were provoked by a pessimistic paper reporting a higher than expected incidence of off-target effects in 2017.[107] This led to what it is probably not unreasonable to describe as a backlash from other researchers, who criticised the experimental design in the reported research.[108] Then, months after publication, the paper was retracted by the journal.[109] The second concern stems from the prevalence of NHEJ compared to HDR repairs and was highlighted by a paper reporting efficient editing and HDR-mediated repair.[110] This finding was quickly criticised as the authors had failed to provide evidence of HDR having taken place.[111] The reason for highlighting these controversies here is not to undermine the credibility of the scientists involved. On the contrary, the public prosecution of these disputes shows science working as it should, and working effectively, through sharing of knowledge, testing and falsification of results, leading to refinements of the techniques used. All of this serves as a useful reminder that this research field is still very much in its infancy and is one that shows both great promise and great uncertainty.

2.14 Research has also identified potential challenges for the clinical use of techniques that rely on DSBs because they activate the tumour suppressor protein, p53, which triggers cells to arrest when DNA DSBs are detected.[112] Thus, while CRISPR-Cas9 is more efficient in cells with lower levels of p53 activity, these cells may be more likely to generate tumours under permissive circumstances. The significance of this is unknown, but there is little or no evidence that editing in mammalian embryos results in tumours, even when it occurs at a high efficiency.

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[105] A number of point mutations and indels are known to occur naturally at each generation. Likewise, off-target events might not result in adverse effects; whether they do or not will depend on the nature of the change.

[106] Gu B, Posfai E, and Rossant J (2018) Efficient generation of targeted large insertions by microinjection into two-cell-stage mouse embryos *Nature Biotechnology* published online 11 June, available at: https://www.ncbi.nlm.nih.gov/pubmed/29889212.

[107] Schaefer KA, Wu W-H, Colgan DF, *et al.* (2017) Unexpected mutations after CRISPR-Cas9 editing *in vivo Nature Methods* **14(16)**: 547–8.

[108] Criticisms included, for example, that it used a prototypical Cas9 rather than rationally redesigned variants with improved fidelity and with which no off-target cleavage has been detected, which would be strongly favoured for clinical applications. 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; Slaymaker IM, Gao L, Zetsche B, *et al.* (2016) Rationally engineered Cas9 nucleases with improved specificity *Science* **351(6268)**: 84–8.

[109] The retraction notice was published on 30 March 2018 and is available at: https://www.nature.com/nmeth/journal/v14/n6/full/nmeth.4293.html#correction3. Not all of the paper's authors agreed with the retraction, but those who did explained the reasoning in a *bioRxiv* preprint (see: Schaefer KA, Darbro BW, Colgan DF, *et al*. (lead author Mahajan VB) (2018) Corrigendum and follow-up: whole genome sequencing of multiple CRISPR-edited mouse lines suggests no excess mutations *bioRxiv* 154450.

[110] Ma H, Marti-Gutierrez N, Park SW, *et al.* (2017) Correction of a pathogenic gene mutation in human embryos *Nature* **548(7668)**: 413–19. In this study, led by US scientist Shoukhrat Mitalipov, the repair mechanism proposed by the authors was that cleavage of the unique CRISPR-Cas9 paternal genomic target was repaired by the non-targeted homologous maternal chromosome.

[111] The critique was led by a preprint publication posted on *bioRxiv*. See: Egli D, Zuccaro M, Kosicki M, *et al*. (2017) Inter-homologue repair in fertilised human eggs? *bioRxiv* 181255.

[112] Haapaniemi E, Botla S, Persson J, *et al.* (2018) CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response *Nature Medicine* published online 11 June, available at: https://www.ncbi.nlm.nih.gov/pubmed/29892067; Ihry RJ, Worringer KA, Salick MR, *et al.* (2018) p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells *Nature Medicine* published online 11 June, available at: https://www.ncbi.nlm.nih.gov/pubmed/29892062.

Genome editing strategies for different purposes

Targeting known variants

2.15 The most straightforward approach conceptually to influencing heritable characteristics (though not technically straightforward by any means) is to edit the genome of an early embryo (called a zygote) to alter a specific variant of the genome sequence.[113] As the cells of the embryo divide and differentiate, the edited version of the genome would then be replicated in all of the cells of the developing organism. Perhaps the most plausible application for this would be cases in which the variant predisposed whoever had it to a clinically recognised disease. In this case, it would be necessary to know before the embryo was created that there was a likelihood of it inheriting the disease-causing variant, such as by screening the prospective parents. (In some cases, they might have been alerted to the possible presence of the variant though having an affected relative and through cascade screening.) In order to allow access to embryos for the purpose of editing them, these would be created in a laboratory using a method of IVF.[114] CRISPR-based genome editing systems might be applied in this context to replace the disease-causing variant, insert a non-disease-causing variant, cause the cells to skip the affected region so that they produce a shorter but still functional protein (exon skipping) or, for cases in which the variant involves a single nucleotide, convert the variant by base editing. These techniques have been demonstrated in both animal models and human preimplantation embryos.[115] This procedure is depicted in the 'Strategies for genome editing in human reproduction' diagram below ('Edited embryos used in IVF/ICSI').

2.16 A limitation of this procedure is that any cell that is to contribute to the living organism cannot at present be subject to genome sequencing, since current testing procedures result in the destruction of the cell. This means that where the editing is carried out in a single-cell zygote (to ensure that the edited genome is replicated in all cells that descend from that first cell), the variation must be diagnosed prior to fertilisation (i.e. in the prospective parents or precursors of the gametes that produced the zygote). If an embryo produced by gametes taken from prospective parents were to be tested to diagnose the presence of a spontaneous variation prior to editing, the embryo would have to have a sufficient number of cells to survive the removal of the cell that is needed for testing. By that stage of development, however, it would have become a significant challenge to deliver the edit efficiently to the remaining cells, especially if mosaicism (where the organism contains cells with different variants) is to be avoided.[116] Even if the edit is made close to the time of fertilisation and, after a number of cell divisions, a cell is removed to confirm the edit has been successful, the presence of the altered variant

[113] Editing gametes (sperm and eggs) prior to fertilisation is also conceivable. Sperm and eggs are haploid cells that each contribute approximately half of the genetic endowment of the future embryo. However, the way in which the genetic material is packaged in mature gametes makes them relatively inaccessible for editing, so embryo editing currently appears to be the more feasible strategy.

[114] IVF is a complex and uncertain method in which a woman typically undergoes a series of non-trivial medical procedures, in the course of which hormones are used to stimulate her ovaries to produce large numbers of eggs, which are then surgically recovered and fertilised in the laboratory with sperm provided by her partner. The fertilisation procedure would involve the injection of a single sperm into each egg (intracytoplasmic sperm injection – ICSI). At around the same time, the editing machinery would be introduced to enable it to access the DNA at a stage when this is amenable to the CRISPR-Cas9 editing activity. After a number of days of development in the laboratory, and after testing one or more cells to check the efficiency and specificity of the editing procedure, the resulting embryos would then be transferred to the woman with the aim of establishing a pregnancy.

[115] See: Perry ACF and Wakayama T (2002) Untimely ends and new beginnings in mouse cloning *Nature Genetics* **30(3)**: 243–4.

[116] The possibility of mosaicism may not constitute a knock-down objection to editing in all cases so long as there is a sufficient population of cells with the non-disease-causing variant to secure the health of the organism as a whole.

(and absence of other differences) in the other cells that remain part of the embryo can only be inferred from the cell that is tested, since these other cells cannot be tested directly. Therefore, the possibility of mosaicism could not be ruled out, especially if the edit has to be delivered to multiple cells in a multicellular embryo.[117]

2.17 Several factors, however, mitigate these concerns. First, it is arguably unlikely that HDR-mediated editing procedures will be licensed until they have negotiated a stringent threshold of efficiency, rendering mosaicism unlikely. Already, work on the mouse suggests that this might be achievable.[118] Second, in all but the rarest cases, even were mosaicism to occur, it would result in a clinically improved outcome compared to no editing at all. Editing a 'healthy' variant would, in effect, replace it with itself and thus be neutral, indicating that, in this regard, an excess of editing components might be permissible, thereby reducing mosaicism. Thirdly, it may one day be possible to edit gamete precursors, enabling confirmation of the desired edit in *all* gametes (or all of their precursors) prior to fertilisation.

Targeting multiple variants

2.18 While small DNA variations, often single base changes, account for a significant proportion of Mendelian disorders, many other disorders and characteristics are associated with variations in multiple sites on the genome and their interaction with environmental conditions. Making multiple changes is considerably more challenging than editing single target sites in the zygote using techniques that cause DSBs in DNA. This is because if multiple DSBs coexist during the finite (hours-long) lifetime of a zygote, it is possible for the DNA ends to join randomly and produce unintended rearrangements. The likelihood of this occurring may increase with the number of DSBs and their relative proximity, and possibly also in a manner that is influenced by specific characteristics of the particular zygote. Too many breaks could trigger programmed cell death (apoptosis) as a response to significant DNA damage.[119] In the mouse, up to eight zygotic alleles have been successfully edited in one step.[120] For complex, multifactorial conditions, a challenge would be to select which one or few of the contributory factors to target out of the many associated with the condition.

2.19 Rather than modifying the nuclear genomes of zygotes or embryos, an alternative strategy to achieve multiple genomic alterations could be to engineer cells with the desired variants before causing them to become sperm or egg cells. The starting point for this could be the cultivation of stem cells, which are the undifferentiated precursors of the many specialised cell types that comprise multicellular organisms. Induced pluripotent stem (iPS) cells can be derived in the laboratory from cells collected from probably any donor. The iPS cells can be cultured for prolonged periods and characterised by whole-genome and whole-epigenome sequencing to confirm the presence of intended edits and the absence (genome-wide) of unintended (off-target) alterations. Other tests could also be applied to meet safety standards required for clinical use. Because the cell populations could undergo successive rounds of culture, editing and characterisation, arbitrarily many edits could, in theory, be achieved and a

[117] Testing DNA from single cells has significant limitations.
[118] Gu B, Posfai E, and Rossant J (2018) Efficient generation of targeted large insertions by microinjection into two-cell-stage mouse embryos *Nature Biotechnology* published online 11 June, available at: https://www.ncbi.nlm.nih.gov/pubmed/29889212.
[119] Concerns about such unintended rearrangements only apply where DSBs occur; multiplex editing by base editors, for example, would not be limited in this way because no DSBs are involved.
[120] It may speculatively be possible to avoid undesired end-joining by suspending zygotic development and introducing single edits sequentially, or just a few at a time.

large number of cells tested at each stage to give confidence in the outcome. Once the desired edits had been achieved, it could be possible (again in theory) to cause the cells to differentiate into gametes or their functional equivalents. If this were achieved, these could then be used to create an embryo carrying the desired genomic alterations.[121] This procedure is depicted in the 'Strategies for genome editing in human reproduction' diagram below ('Edited iPS cells give rise to precursor cells').

2.20 A procedure such as the one described above would depend on advances in producing functional gametes from stem cells. This is a current area of research that has potential as a treatment for infertility where the patient cannot produce functional gametes (e.g. as a result of treatment for cancer). Both male and female gamete-like cells have been produced in mouse models starting with iPS or embryonic stem (ES) cells and leading to full-term development of progeny. Mice produced following male meiosis *in vitro* were apparently healthy, but many of those generated after female meiosis were abnormal.[122] There may be technical challenges, however, in translating this research into humans, and even if these formidable technical hurdles are overcome, the use of iPS cell-derived gametes is likely to raise additional issues to compound those raised by genome editing alone.[123]

2.21 An alternative strategy could be envisaged that would similarly involve multiple rounds of autologous stem cell culture, modification and characterisation, followed this time by the transplantation of gamete precursor cells (spermatogonia and oogonia) back into the cell donor (or, in theory, another recipient).[124] Once back in the donor's body, they might be capable of giving rise to mature gametes. In the case of sperm precursor cells (in the case of the male), if the recipient were rendered infertile prior to the cell transplant, gametes that he produced after the transplant should all carry the altered genotype, potentially allowing him to conceive with a female partner without having to undergo assisted conception treatment. The process of transplanting spermatogonial stem cells to yield mature, functional sperm has been demonstrated in rhesus macaques.[125] This procedure is depicted in the 'Strategies for genome editing in human reproduction' diagram below ('Edited sperm precursor cells implanted into testes').

Modifying gene expression

2.22 An alternative to editing the genome is to modify its activity in a way that does not alter the genome sequence. It is possible, for example, to 'silence' a given gene whose product is detrimental to the organism by targeting an alteration to the epigenome (by methylation and acetylation of histone groups that package DNA to prevent damage and control gene expression and replication).[126] Compared to the genome, little is known at

[121] A similar strategy using *in vitro*-derived eggs has been proposed as a means of avoiding inherited mitochondrial disease; see: Greenfield A, Braude P, Flinter F, *et al*. (2017) Assisted reproductive technologies to prevent human mitochondrial disease transmission *Nature Biotechnology* **35(11)**: 1059–68.

[122] Hikabe O, Hamazaki N, Nagamatsu G, *et al.* (2016) Reconstitution *in vitro* of the entire cycle of the mouse female germ line *Nature* **539(7628)**: 299–303.

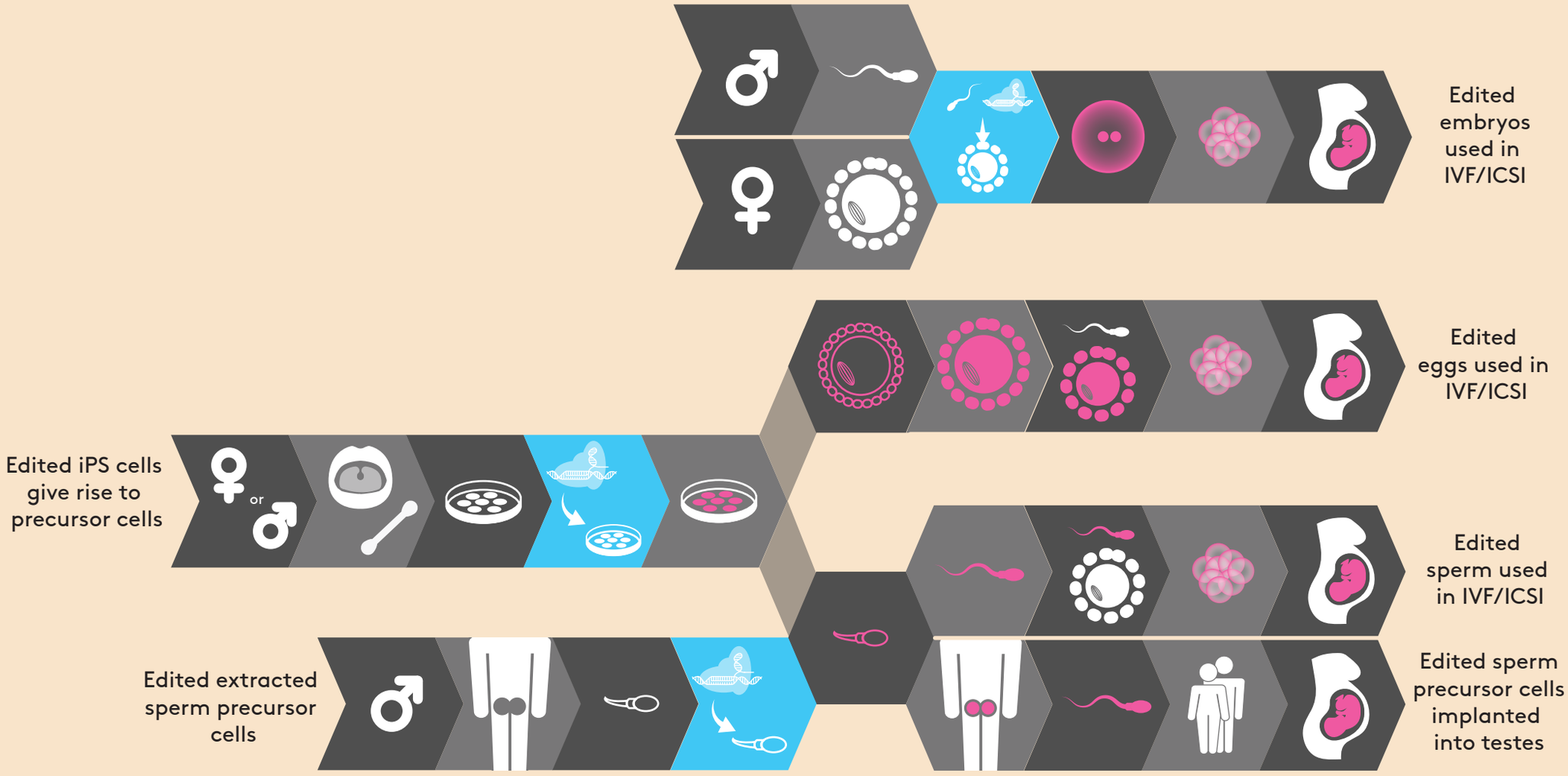
[123] See: Smajdor A and Cutas D (2015) *Background paper: artificial gametes*, available at: http://nuffieldbioethics.org/wp-content/uploads/Background-paper-2016-Artificial-gametes.pdf; for more recent developments, see: Boiani M (2017) Call for papers: *in vitro*-generated germ cells – facts and possibilities *Molecular Human Reproduction: Basic Science of Reproductive Medicine* **23**: 1–3.

[124] The procedure would be significantly less challenging if begun with retrieved spermatogonial stem cells.

[125] Hermann BP, Sukhwani M, Winkler F, *et al.* (2012) Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm *Cell Stem Cell* **11**: 715–26.

[126] See, for example: Saunderson E, Stepper P, Gomm J, *et al.* (2017) Hit-and-run epigenetic editing prevents senescence entry in primary breast cells from healthy donors *Nature Communications* **8**: 1450.

Strategies for genome editing in human reproduction



present about the inheritance of epigenetic marks. Epigenetic modification might, however, allow alterations that are intergenerational (affecting the next generation) but not transgenerational (being passed on to subsequent generations indefinitely), such that the subsequent generation reverted to the grandparental characteristics. In some lights, possibly including the posited intergenerational epigenetic inheritance of obesity, this might be seen as an advantage of the approach.[127] Epigenetics is an active area of research from which advances in understanding can be expected.

2.23 The procedures described above, while possible in theory and supported, to varying extents, by existing research, would have to overcome significant challenges, both technical and ethical, before they could ever be attempted in humans. It is implicit throughout that these approaches should be seen in the context of other non-reproductive strategies (e.g. post-implantation or post-partum somatic gene therapy) that may make their development redundant or supplant them, and in the context of other reproductive options that may be feasible and available (e.g. using gametes from a donor with the desired genetic characteristics). We will return to this question of the broader context framing the challenge in a later section of this chapter.

Genomics research

2.24 One of the current factors limiting the potential utility of genome editing is the available knowledge about human genomes and the implications of genetic variation. Although we now know a great deal about the genetic factors that are implicated in many diseases, for many characteristics, we know comparatively little as yet about how genetic variations (or combinations of variations) contribute to them (and therefore how to influence those characteristics through genetic modification). To be able to move beyond influencing only single gene disorders, there seem to be three separate kinds of technical problem to be overcome. These are problems that are addressed by genomics research, which could be summarised as: (1) a technology problem; (2) an information problem; and (3) a utility and risk problem.

- The technology problem is the limitation on the capacity to sequence genomes accurately and cost-effectively and to manage the huge amounts of data involved in genome assembly.
- The information problem concerns the difficulty of obtaining sufficient biological information to allow understanding of the underlying genomic factors associated with differences in biological function or the reliable prediction of the effect of a genome modification.[128]
- The utility and risk problem concerns the possibility of using the knowledge obtained to make a change in the organism that would have the precise desired effect and, at the same time, no undesirable collateral effects.

This section will summarise our findings with regard to the importance and prospects of genomics research in identifying actionable targets for genome editing strategies.

[127] A significant set of concerns expressed in the literature relates to the transgenerational nature of DNA editing – the fact that modifications will be passed down to all future generations in perpetuity unless some further modification overwrites them. It has been observed that this closely reflects the process of evolution that has led to the present stage of development, and it has been further observed that if a modification can be made successfully in one direction, a reversal modification should also be achievable, if desired, at the next generation.

[128] See: Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biological research and health care: ethical issues*, available at: http://nuffieldbioethics.org/project/biological-health-data.

Genome sequencing

2.25 Developments in sequencing technology are being driven by 'Big Science' initiatives in biomedical research, but also in other biological fields and new generations of sequencing technologies. At present, a number of these initiatives are generating whole-genome sequences. From the evidence we have taken, it seems safe to assume that no technological limits will halt the current trends in genome sequencing of declining cost and increasing speed and completeness. The cost of clinical-quality genome sequences will probably continue to fall so as to become effectively available to anyone in the industrialised world.[129] This may not mean, however, that everyone or even a large proportion of people on the planet will have a personal genome sequence determination or that benefits to human health will necessarily follow. Where large proportions of the global population, even in industrialised countries, are struggling with poverty and social inequality, genome sequencing may be far from a priority.[130] Many people may simply decline or refuse to have their genomes sequenced for reasons of privacy, and there may be limitations on access to genome sequence data for similar reasons. Furthermore, policy and regulatory hurdles may intervene and genome information may be limited by ancillary technologies (data storage, management, governance, etc.).

Annotation and interpretation

2.26 What is harder to determine is what the limits might be to the biologically useful knowledge that can be derived from genome sequence data.[131] Opinion has it that there are unlikely to be intractable computational limits to discerning gene function if sufficient data are available. It is questionable, however, whether sufficient data are or could ever be available to unravel the contribution of genetic factors to all observable biological characteristics. These data might be, for example, from the manipulation of animal models or high-quality empirical data (e.g. 'deep' phenotype data) corresponding to given genome sequences.

2.27 A major component of this limit may be complexity. Although new methods are helping with the study of the effects of genomic variation in model systems in the laboratory, the multiplicity of factors and the complexity of the relationships involved make unravelling the function of variation in humans much more challenging. There may not be, and may never be, a sufficient number of people to provide data with which to unravel the precise contribution of each sequence variation and the set of biographical and environmental conditions in which it is manifest. Such limits may be encountered in the future; at present, the scale of what we can usefully know remains largely uncertain.[132] The prospect of encountering a limit has not forestalled the appearance and growth of companies proposing to apply machine learning to the genome in order to identify the

[129] The current limit for high-throughput short-read sequencing seems to be the chemistry involved in the genome amplification, rather than the computational power required for assembly. (Long-read technologies will probably do this better.) The chemistry currently takes approximately six hours for a human genome; current supercomputers can run software that can assemble a whole human genome in eight minutes, but with greater parallelisation, this could probably be reduced to four minutes. This depends, of course, on what is meant by a 'genome' – no genome is definitive.

[130] Although it could conceivably become a priority, for example, in the case of a public health emergency, such as an epidemic.

[131] The utility of this knowledge is, of course, not restricted to identifying genome editing targets: such knowledge can inform the choice of other therapeutic and lifestyle options (personalised medicine, diet, etc.) and even choice of reproductive partner.

[132] In evidence given to the working party as part of our inquiry, we were told about the need for more 'deep' phenotyping (fact-finding meeting on genome sequencing and genomics, 10 May 2017) and about issues of data quality and interoperability – to the extent that pre-existing data were relatively useless and there is a need to start again with more disciplined data collection (fact-finding meeting, 5 October 2017). This somewhat deflates the ambitions of repurposing data that animate the 'big data' paradigm (and that lie behind the ambition of the UK life sciences industrial strategy to capitalise on the supposedly unparalleled data resources of the NHS). See: Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biological research and health care: ethical issues* available at: http://nuffieldbioethics.org/project/biological-health-data.

likelihood of a range of complex observable characteristics from the onset of individual development.[133]

Box 2.1: Genome-wide association studies

Genome-wide association studies (GWAS) involve comparing genome sequences from members of a cohort to see whether the sequences correlate with any given trait or traits. Because GWAS compare variations across the genome, they offer a possible way to identify complex diseases in which many genetic variations are implicated. This approach has been used to identify small genetic variations associated with diabetes and Parkinson's disease, as well as genetic factors affecting drug reaction and susceptibility to certain environmental conditions. GWAS findings have been used to estimate individual disease risk, and this is an area of developing knowledge.[134]

Interdependence and independence

2.28 A further consideration is the extent to which knowledge of functional genomics will mean that inheritable characteristics will be tractable to genome editing strategies. It may not only be limited by the complexity of contributory conditions for a given characteristic, but also by the complexity of functions a given genetic factor may have in the organism and how it might interact with other genetic and non-genetic factors, such as in different systems, tissues or conditions. Many genome sequences have multiple functions (pleiotropy) that may vary depending on, for example, the time or tissue in which they are expressed, the developmental stage and factors with which they or their products synergise directly or otherwise. While it may be possible to say that a given genome sequence regulates a particular observable characteristic, it may nevertheless not be possible to alter this sequence without affecting a gamut of other characteristics, possibly in ways that are incompatible with well-being or survival.

2.29 Most significantly, the relative contribution of genetic factors compared to other factors, such as environment, for many of the characteristics that people may wish to influence may be slight to negligible. (The belief that disease states, characteristics and behaviours are in most cases dependent on the presence or absence of particular genetic factors – genetic determinism – has tended to be strongly qualified in measure with the increase in knowledge of genomics). At present, it is therefore difficult to predict with any confidence whether the cases in which we might influence inherited characteristics by genome editing will be widespread or relatively rare, important or trivial. It may turn out that the uses of genome editing will be limited to single gene disorders and a few simple, well-characterised risk factors. While we cannot know at present how much more it may be possible to achieve, the absence of a definite constraint makes it reasonable to give consideration to what remains within the scope of possibility.

[133] See, for example, the mission statement of the company Genomic Prediction, whose claim is that "Our approach reduces disease risk and improves newborn health outcomes by identifying candidate embryos for implantation which are genetically normal." See: https://genomicprediction.com/.

[134] The US National Human Genome Research Institute and the European Bioinformatics Institute jointly maintain a *Catalog of published genome-wide association studies*, available at: http://www.ebi.ac.uk/gwas/.

Possible pathways of technological development

2.30 In this section, we will move on from the development of genome editing techniques in a research setting to the emergence of genome editing as a prospective biomedical technology. The transition from promising research technique to a usable technology involves the assembling of knowledges, practices, products and applications.[135] In the first part of this chapter, we have discussed technical developments and some of the kinds of knowledge required for genome editing to be able to influence inherited characteristics. We now turn to some other contingent conditions. These include contextual factors that 'pull', 'push' and 'shape' the technology in development, factors like demand for the technology, its attractiveness to financial investment, institutional and public policy, legal and regulatory norms, public interest and developments in the global context.

2.31 As long as we merely describe the science of genome editing, developments appear to follow a more or less linear path, notwithstanding the inevitable setbacks and occasional forward leaps that are characteristic of scientific practice. From the perspective of the technique, the course of its evolution can be imagined as a series of stages from discovery and verification, through development, validation and translation or innovation, to embedding as technical change. Standing back from this and looking at genome editing as, for example, a historian of the future might do, the path might look as though it is navigating a more complex terrain, full of false trails and dead ends, obstacles and detours. Such a history would probably reveal that the significance of most discoveries turns out to be not what it might at first have appeared, that most inventions do not lead to the outcomes initially hoped for and that most promising innovations fail.[136] Situated as we are in the midst of this unfolding history, we are faced with significant uncertainties.

2.32 By taking a broad view, we can nevertheless try to make comprehensible the processes by which technological development can be diverted along different pathways, sent down dead ends and co-opted to new purposes. Taking such a broad view will, however, require that we cease to regard the emergence of genome editing technology as the unfolding of a series of developments solely according to scientific method. Better understanding the process may not help to predict the outcomes with any more certainty. What is gained by acknowledging the effect of contingent conditions is the illumination of underlying (typically unstated) assumptions, constraints and mechanisms of the innovation system, leading to the identification of possible sites and opportunities for more constructive governance, prioritisation and control.

Entry points and near-term and longer-term uses

2.33 Among the cases that would constitute good reasons for developing genome editing technologies to influence inherited characteristics in future people, there seem at first blush to be few that relate to single gene disorders. Prenatal and preimplantation genetic testing offer ways of avoiding inherited disease in all but extremely rare and complex

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

[136] The success or failure of inventions is often due to contingent factors such as commercial viability or opportunity, rather than any technical feature. As we noted in *Emerging biotechnologies: technology, choice and the public good*: "the *origins* of invention seem rarely to be found in *plans* for invention and the uses of resulting inventions are often very different from intended uses." In the case of CRISPR, described by Franciso Mojica in 1993, its potential as a programmable tool took nearly 20 years to emerge: Edgerton D (2011) *Shock of the old: technology and global history since 1900* (London: Profile books); Marvin C (1990) *When old technologies were new: thinking about electric communication in the late nineteenth century* (New York: Oxford University Press).

cases. The cases in which genome editing offers the *only* option of having a genetically related child while excluding a specific condition (i.e. where a given couple could not conceive a child who did not inherit that condition) are probably very rare.[137] According to our current understanding, they would be limited to:

- Y chromosome defects
- inversions and deletions of chromosome segments
- dominant genetic conditions, such as Huntington's disease, some forms of Alzheimer's disease or breast cancer, where one of the prospective parents is homozygous[138]
- recessive genetic conditions where both parents are homozygous[139]

2.34 There are, however, potentially many more cases in which the likelihood of any embryo conceived by the prospective parents having the genetic characteristics sought is low. Using genome editing in these cases could therefore substantially increase the chances of having a child following assisted reproduction treatment compared to preimplantation genetic diagnosis, in which a number of embryos may be discarded. (The chances of having a child in any given cycle of fertility treatment may be low in any case and dependent on a range of other factors, such as maternal age, which may affect all reproductive projects, as well as any collateral effect that the genetic condition to be avoided may have on fertility). Such cases include:

- dominant genetic conditions where both parents are heterozygous for the predisposing variant (on average, only 25 per cent of embryos will be unaffected) or where one parent is heterozygous for the predisposing variant and the other carries the common variant (in which case 50 per cent of the embryos will be unaffected on average)
- recessive genetic conditions where one parent is homozygous and one heterozygous (50 per cent unaffected)
- where the aim is to exclude/include a condition that is associated with two or more independently assorting genetic variants (which will multiply the odds against any embryo they conceive having the characteristics sought) or two or more characteristics associated with single variants that assort independently[140]

2.35 We said above that, other things being equal, for almost all known genetic diseases there are existing alternative reproductive options available. This must now be qualified in two important ways. Firstly, whether these alternatives are to be regarded as meaningful equivalents is not a simple question: it will depend on a background of assumptions, understandings and values that can be argued out in different ways. People might have strong personal reasons for preferring or objecting to different forms of assisted conception treatment, for example. Secondly, all other things are *not* equal: as we observed in Chapter 1, choosing an available donor might involve an unacceptable compromise in terms of donor characteristics. (It is certainly possible that people with desirable characteristics may not be available as donors: donation is a voluntary act and donors have interests in the use of the gametes they donate, although in the UK these

[137] This assumes that first-degree genetic relatedness is a necessary criterion (otherwise alternatives of gamete/donation, etc., still apply). Some degree of genetic relatedness could be preserved by intra-familial gamete donation, which is practised, although it creates distinctive psychosocial challenges.
[138] Such cases are very rare in the general population and it is likely that the parent themselves would be affected, although they might be seen more often in couples who are closely related (e.g. where cousin marriage is practised).
[139] As above, such cases are rarely seen in the general population, but may occur with higher frequency in some groups.
[140] An example is the selection of a future child who is both not affected by an inherited disorder and has an appropriate tissue type to enable them to act as a tissue donor for an existing, affected sibling (so-called 'saviour siblings').

do not extend entitlements to information about or contact with any resulting offspring.[141]) Furthermore, it might not be reasonable to expect sufficient viable embryos with the characteristics sought to be available.

2.36 Were genome editing to be developed for intractable cases of heritable disease in which there is no alternative way of having a genetically related child without the disease, it might have little direct relevance to most people. However, there are many more potential uses of genome editing than these. Setting aside for the moment any scruples relating to the nature of the techniques themselves and their further implications, it is possible to imagine how genome editing could come to displace incumbent technologies like preimplantation genetic testing, even where these remain viable 'alternatives'. Furthermore, there is a class of conditions – increasingly revealed by genome sequencing – that are relatively common in populations. The occurrence of these conditions is less easy to predict, and also harder to avoid through selective approaches (of partners or gamete donors, of pregnancies to continue or embryos to transfer). Therefore genome editing could be used to exclude genetic factors predisposing to:

- Complex diseases, where there is a significant risk of later morbidity or mortality requiring intrusive or invasive treatment, or where later treatment would or might be ineffective.

2.37 We have moved from the theoretical consideration of very rare cases of serious disease in which all genetically related offspring would inevitably be affected from an early stage of life to relatively common cases of serious disease risk in which all genetically related offspring might be affected at an early or later stage of life. Here, particularly given current limitations in knowledge, the situation is complex: depending on the condition, the genetic factors may be multiple and their significance uncertain, they may interact with environmental factors in ways that are hard to isolate or control or the known genetic risk factors may lack penetrance so a person with all of those factors may live a full life unaffected by the condition while a person who lacks those factors might be affected nonetheless. In this case, genome editing is not an alternative to forgoing the chance of having a genetically related child who is not affected by a serious disease in childhood, but rather an alternative to the possibility that a future child will have a potentially life-limiting disease, sooner or later requiring invasive and undependable treatment. Here, the options might involve balancing different kinds of risk (or exchanging known risk for unquantifiable uncertainty) rather than eliminating risk of disease altogether. As we observed in Chapter 1, genomics research is increasingly revealing that there is no perfectly 'healthy' genome.

2.38 We can now also begin to ask a different sort of question. Rather than considering what might constitute a good reason to develop genome editing technologies to influence inherited characteristics in the first place, we should begin to consider what a future in which genome editing technologies are available would be like. Were such technologies to prove themselves safe and effective enough for clinical use for some initial indications,

[141] The donors' interests are exercised principally through giving or withholding consent to the use of their gametes, which may be given subject to conditions (although clinics may decline to accept as donors people who place restrictive, unreasonable or discriminatory conditions on the use of their gametes). Under the Human Fertilisation and Embryology Act 1990 (as amended), donors are entitled to apply to discover whether any children have been born as a result of their donation and, if so, how many and the sex and year of birth of each. At the age of 16, donor-conceived people may apply to the Human Fertilisation and Embryology Authority to discover non-identifying information about the donor and, at 18, where the information was provided by the donor after 31 March 2005, they may discover the donor's identity.

we can ask what other outcomes of positive value we might be able to achieve. This opens up a new range of possibilities that include, but are certainly not limited to:

- built-in genetic resistance or immunity to endemic disease[142]
- tolerance for adverse environmental conditions (such as those that might be envisaged as a result of climate change or in space flight)
- supersenses or superabilities[143]
- other factors that are likely to improve welfare (however defined), such as the facility to expand dietary options (ranging from lactose tolerance to obtaining nutritional benefit from substances that are not usually eaten by humans or the ability to make vitamins rather than having to ingest them

2.39 What opens up these possibilities is a change in perspective from one focused on the achievement of a limited purpose – one that may have animated the initial research and innovation – to a vision animated by the exploitation of a technology to secure the maximum value from its use. Given that genome editing implies the capacity to edit almost any DNA molecule and that DNA is fundamental to biological systems in general, this capacity for exploitation is something that genome editing potentially shares with other technologies that have very general application, from the steam engine and the electronic computer to satellite and nuclear technologies.[144] Such technologies are often hailed as revolutionary or age-defining ('industrial revolution', 'information revolution', 'space age', 'nuclear age', etc.), as they are claimed not merely to increase productivity, but to spawn entirely new industries and produce a rupture with what has gone before ('post-genomic'). It is implicit that, in doing so, they reconfigure the social relations in which they are embedded. Before getting carried away, however, we should recall that only relatively few characteristics are strongly determined by genetic factors that have been identified by genomics research, and the genomic contribution to many characteristics that may be highly complex is relatively slight compared to other factors.

Funding, finance and momentum

2.40 Though the emergence of genome editing technologies might well, in the first instance, lead to applications to avoid a small number of rare diseases, these may not exhaust the reasons for developing those technologies. The prospect of the further exploitation of the technology for a range of more common challenges suggests a prize that might justify the high cost of the resources required to develop any of the genome editing strategies described. Further applications are, however, less often articulated and much more

[142] One of the first reported experiments with genome editing in human embryos was to introduce a *CCR5Δ32* allele, which is protective against HIV infection, into tripronuclear embryos (see: 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). Although HIV has proved relatively stable, viruses can mutate rapidly, so this strategy may be of limited use in many cases. Further knowledge of other pleiotropic effects of the variants is also needed.

[143] Some of these possibilities were raised in the online questionnaire that was published as part of the evidence-gathering activities supporting this project (see Appendix 2 below). The purpose of the questionnaire was to test the views of a range of individuals about others' reproductive decisions: how people felt and reasoned about some of the things others might wish to do and where, if anywhere, they thought it was reasonable to limit these projects. For the majority of respondents, the difference in acceptability between using genome editing to avoid having a child with a genetic disease and using it to have a child with other traits that would not immediately affect their well-being was not as marked as might have been expected. Although the respondents to our questionnaire were in no way representative of the wider population, this finding nonetheless merits further exploration in the light of our framing of questions about genome editing in human reproduction as being about the fulfilment of reproductive desires rather than the elimination of disease.

[144] There is debate in the literature about the description and impact of 'general purpose technologies'; see: Jovanovic B and Rousseau PL (2005) General purpose technologies, in *Handbook of economic growth* Aghion A, and Durlauf S (Editors) (Amsterdam: Elsevier), pp 1181-224.

uncertain. There is a disconnection between the cases that are put forward as the most likely for innovation and the much wider range of cases that may afterwards account for diffusion of the technology. One reason that these latter cases do not appear as drivers of the technology is that attention to date has been focused on the underlying science as distinct from its more worldly context. Research on human embryos to date is often presented as 'basic' research, the objects and aims of which are distinct from those of applied research and development. Indeed, it is entirely plausible that the motives of the individual researchers involved have more to do with the pursuit of knowledge and scientific excellence, professional recognition and reward than with any 'downstream' social impact.[145] Furthermore, if the aim is 'basic' research, the question of the substantial opportunity cost of devoting significant resources to developing techniques with limited or uncertain application (which might, in theory, be redeployed in other priority areas of research) need not arise. If instrumental value is set aside, the excellence of research *as research* becomes a more significant criterion of evaluation.[146]

2.41 The 'basic/applied' research distinction, in fact, corresponds to a division of responsibilities that underlies the kind of innovation systems that are characteristic of many technologically innovative liberal democracies in which free market economic considerations play a role.[147] The expectation underlying such systems is that publicly funded scientific research (often equated with *academic* research) fills up a reservoir of intellectual capital from which commercial entrepreneurs may draw to develop useful innovations for which they are rewarded in the marketplace.[148] These, in turn, increase productivity and thereby generate economic growth and national well-being. The underlying aim is essentially to balance risk and reward between public and commercial research in a way that generates the greatest productivity, although this balance can be significantly affected by cultural and other factors.[149] Though this model arose originally in relation to industries based on physical and chemical sciences, the rhetoric has readily transferred to biological sciences, perhaps with the distinction that, in the domain of biomedical research, the goal of improved well-being is sometimes more prominent than that of economic growth.[150] While this model has significant shortcomings as a description of innovation in practice, the governance of biomedical research and

[145] See: Nuffield Council on Bioethics (2014) *The culture of scientific research: the findings of a series of engagement activities exploring the culture of scientific research in the UK*, available at: http://nuffieldbioethics.org/wp-content/uploads/Nuffield_research_culture_full_report_web.pdf.

[146] Quite evidently, research resources (including the knowledge, skills and interests of individual researchers) are not fungible commodities. The self-referential approach of funding excellent research (which survives in the UK Research Excellence Framework) has often been associated with the so-called 'Haldane principle' on the implicit basis that, since it cannot be known which basic understanding of nature it will be useful to produce, the production of all knowledge has an equal claim to support. In reality, successive governments have been more or less *dirigiste* with regard to research funding, and different sorts of criteria (e.g. anticipated strategic and economic value) have been applied to basic funding allocation decisions between different areas of scientific research (e.g. between the biological and physical sciences).

[147] The distinction between basic and applied research was formulated in the 1960s by the Organisation for Economic Co-operation and Development for statistical and comparative purposes. (Organisation for Economic Co-operation and Development (1981) *The measurement of scientific and technical activities: proposed standard practice for surveys of research and experimental development: 'Frascati manual' 1980*, available at: https://www.oecd.org/sti/inno/Frascati-1981.pdf). It has been used by liberal thinkers to defend science from interference and subservience to political and economic objectives (see, for example: Polanyi M (2000) The republic of science: its political and economic theory *Minerva* **38**: 1–21). The distinction between basic and applied or preclinical research was emphasised by many of the early scientist-led position papers following the emergence of CRISPR-Cas9 genome editing.

[148] On the fallacy of equating science with academic research, see: 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 and Worms N (Editors) (New York: Watson), pp 1-36.

[149] There are considerable differences in national innovation systems, even those formally regarded as democratic. For example, South Korea's innovation system is very 'top-down', driven by a cultural mindset that is still steeped in military rule and in which bureaucratic permission is still required. At the same time, cultural attitudes towards risk are very conservative, so it is difficult to motivate young university graduates to establish start-ups and pursue entrepreneurial activity: they prefer to play it safe in the large conglomerates ('chaebols').

[150] Biology became 'big science' with the Human Genome Project, and successive life sciences strategies have adopted the rhetoric of economic growth and international competitiveness.

innovation, which manages risk through incrementally staged and regulated protocols, is implicitly structured along these lines in jurisdictions such as the UK. This has the implication of potentially insulating the largely academic 'basic' researchers from moral responsibility for how biomedical technologies are developed and applied, which is a matter for translational medicine or, if it is removed from them, for those who fund, govern and (more formally) regulate translational medicine.

2.42 The distinction between 'basic research' and 'applied research' (or between 'underpinning' and 'translational' research, etc.) has been extensively critiqued, notably by scholars involved in the interdisciplinary practice of science and technology studies.[151] They argue that this distinction presents the relationship between knowledge production and technological innovation in a way that is empirically false and that the practice of basic research is always already caught up with the prospect of applications (a view that might be attested to by the swiftness with which biotechnology firms were spun out of the initial research on CRISPR-Cas9 and the aggressive patenting disputes that ensued).[152] Since the financial crisis of 2008, public funding of academic research around the world has shifted significantly away from purely 'curiosity-driven' research and towards applied research.[153] Funding organisations increasingly encourage researchers to focus on the 'impact' of their work. This requires almost all researchers to consider, in advance of funding, perhaps not where their research will lead, but at least where it *could* lead, or *the directions in which* it could lead and *who* might have an interest in taking it up.[154] It also thereby helps to re-engage them with the ethical dimension of research.

2.43 This renewed engagement with moral responsibility has been taken up under the banner of 'responsible research and innovation' (RRI) and incorporated into a number of research funding programmes (such as the European Union's 'Horizon 2020' framework programme).[155] The aim of RRI is to re-engage the practitioners of science with the values and priorities of the societies in which it is practised.[156] As a consequence, willingly or not, leading scientists are projected as social actors (just like business leaders and other significant public figures) and emphasis is placed on the political dimension of research and the practical importance of reflection, deliberation and engaging the public. Although lacking a single, fixed form, taking seriously the idea of RRI has two potentially beneficial consequences. The first is that it encourages a process of reflection that tends to counteract 'technological momentum' (where research objectives can be pursued to the point of unintended consequences). Secondly, it opens up a broader reflection on the relationship between technology and society and how technological solutions may inform societal challenges (and 'crowd out' other socially desirable alternatives).[157]

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[151] For example, Hurlbut JB (2018) In CRISPR's World: Genome Editing and the Politics of Global Science,, in *Routledge handbook of genomics, health and society*, Gibbon S, Prainsack B, Hilgartner S, and Lamoreaux J (Editors) (Abingdon: Routledge).

[152] See Chapter 4 below.

[153] See: UNESCO (2015, revised 2016) *UNESCO science report: towards 2030*, available at: https://en.unesco.org/unesco_science_report.

[154] See: UK Research and Innovation (2018) *Pathways to impact*, available at: https://www.ukri.org/innovation/excellence-with-impact/pathways-to-impact/.

[155] For RRI in Horizon 2020, see: European Commission (2018) *Responsible research and innovation*, available at: https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation.

[156] Hilgartner S, Prainsack B, and Hurlbut JB (2016) Ethics as governance in genomics and beyond, in *Handbook of science and technology studies,* fourth edition, Felt U, Fouché R, Miller CA, and Smith-Doerr L (Editors) (Cambridge, MA: MIT Press), pp.823-51.

[157] See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies; Williams R (2006) Compressed foresight and narrative bias:

Technological determinism and social constructivism

2.44 Technological determinism is the idea that the nature of the technologies in use in a society determine the nature of social relations among people. This idea is often associated with some early works of the philosopher, Karl Marx.[158] Consideration of how modern technology has the capacity to alter the way human beings understand their own distinctive way of existing was notably developed by the philosopher Martin Heidegger in *The question concerning technology*.[159] Heidegger's essay explores the way in which modern industrial technology represents nature and other human beings as mere resources in a way that obscures the essential humanness of their being.

2.45 The counterpoint to technological determinism contends that the rejection or adoption of technology can only be understood or explained through its social context – through, for example, how it satisfies human interests and, in particular, *whose* interests.[160] This social perspective is not, however, incompatible with the idea that technologies can shape the exercise and limitation of human freedoms or that technologies and cultures are co-produced. Thomas Hughes, a prominent social constructivist, has argued 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, as they configure ancillary services around them and create social dependencies.[161] In any case, the fact that technological forms may shape social relations does not mean that they are unchosen. It matters, therefore, that the opportunities for choice are realised at the time; it also matters who does the choosing. One of the key questions addressed in our 2016 report *Genome editing: an ethical review* was that of the 'transformative potential' of prospective genome editing technologies: that they might have the power to shape social relations in this way, specifically the way people relate to each other (interpersonally, intergenerationally) through reproduction.[162]

2.46 There are several technical features of CRISPR-based genome editing that suggest the prospect of reproductive technologies with very general application. These include their flexibility (they can, in principle, be used for all DNA/RNA molecules), effectiveness and efficiency (at making targeted alterations without off-target effects), relative rapidity (typically reducing research time from years to months), relative accessibility (such that they can be used by competent biologists without highly specialised skills) and relative affordability (compared to alternative genetic approaches – although the question of

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pitfalls in assessing high technology futures *Science as Culture* **15(4)**: 327–48; König H (2017) The illusion of control in germline-engineering policy, *Nature Biotechnology* **35(6)**: 502–6.

[158] Marx famously wrote in the second chapter of his 1847 work, *The poverty of philosophy*: "Social relations are closely bound up with productive forces. In acquiring new productive forces men change their mode of production; and in changing their mode of production, in changing the way of earning their living, they change all their social relations. The hand-mill gives you society with the feudal lord; the steam-mill society with the industrial capitalist." But there is a further element, as Marx continues, however: "The same men who establish their social relations in conformity with the material productivity, produce also principles, ideas, and categories, in conformity with their social relations." Marx K (1847) *The poverty of philosophy,* available at*:* https://www.marxists.org/archive/marx/404.htm.

[159] The essay is a version of lectures given by Heidegger in the late 1940s and was first published in printed form in 1954: Heidegger M (1977) The question concerning technology, in *The question concerning technology and other essays*, (trans.: Lovitt W) (New York and London: Garland Publishing, Inc.), p.13. Some of Heidegger's themes were developed and given a more overt moral inflection by his former student, Hans Jonas, whose work achieved some traction in the English-speaking world (possibly owing to the greater accessibility of his work and Heidegger's association with Nazism); see, for example: Jonas H (1979) *Towards a philosophy of technology* (Garrison, NY: Hastings Center).

[160] For social constructivism (or the social construction of technology) see the classic: Bijker WE, Hughes TP, and Pinch T (Editors) (1987) *The social construction of technological systems, new directions in the sociology and history of technology* (Cambridge, MA: MIT Press).

[161] Hughes T (1994) Technological momentum, in Smith M and Marx L (Editors) *Does technology drive history? The dilemma of technological determinism* (Cambridge, MA: MIT Press).

[162] In *Emerging biotechnologies*, we distinguished characteristics of emerging biotechnologies as 'uncertainty', 'ambiguity' and 'transformative potential', the latter characteristic being distinguished from that of being (economically) 'disruptive'.

overall cost compared to other approaches is a complex one).[163] Furthermore, the techniques are continually undergoing development and refinement, so we can expect an increasing rate of diffusion and use. Clearly, there are bottlenecks that require further refinements and parallel developments to be achieved, such as in relation to delivery, multiplexing and efficiency (especially controlling the HDR process). What these factors amount to, however, is the potential for genome editing – particularly CRISPR-Cas9 and further developments of that technique – not only to accelerate biological research, but also to transform the nature and aims of that research, how and where it is practised and by whom.

Public policy, public interest and public morality

2.47 Technologies do not, however, need to be large scale or widely diffused – certainly not from their first appearance – to be socially transformative. What have been called 'transformative technologies' may be insidious rather than revolutionary (we will return to this in Chapter 3 when we consider the potential of genome editing for collateral and unintended effects). If regulation provides a means to control this by imposing an orthodox, managed linearity to the process of research, development and innovation in the biomedical sciences, the application of regulation and its guiding concerns nevertheless (arguably) does not extend sufficiently far 'backwards' into decisions about 'basic' research or project sufficiently far 'forwards', taking into account possible future outcomes, to neutralise the uncertainty and social risks that lead to what has been described as a 'technology control dilemma'.[164] In fact, the linearity imposed by the model governance may even contribute to this dilemma.

2.48 Beyond the scope and the usual preoccupations of regulation lie broader questions about the relationship between technologies and the conditions of life in which people find themselves in contemporary societies. These are questions about public policy, the object of which, at the most general level, is to use the mechanisms of government (ranging from, for example, promotional funding through to legal prohibition of specified activities) to bring about desirable states of affairs for a given society and to avert states of affairs that are considered undesirable.[165] Biomedical technologies raise questions of

[163] The majority of the cost of the service is, at any rate, unlikely to be the editing part of the procedure. The question of price is a separate and even more complex economic question. As Kenneth Taylor, Ilke Turkmendag, Matthias Wienroth and Simon Woods note in their response to our refreshed *Call for evidence*: "Though the technology of genome editing may be cheap, the associated costs of infertility treatment are not (witness the fact that fewer than one in five NHS Trusts fund fertility treatment to the NICE recommended levels)." In their joint response to our refreshed *Call for evidence*, the Medical Research Council and the Biotechnology and Biological Sciences Research Council said: "As with other advanced therapies, the costs will be high in the first instances and many of the challenges found in regenerative and stratified medicine, such as access and cost, will need to be played out".

[164] The difficulty of managing emerging technologies to avoid adverse effects and secure desirable outcomes is often presented as a 'technology control dilemma', originally formulated by the social philosopher, David Collingridge (Collingridge D (1980) *The social control of technology* (Milton Keynes: The Open University Press)). The horns of the dilemma were presented as follows: first, the information problem: "understanding of the interactions between technology and society is so poor that the harmful social consequences of the fully developed technology cannot be predicted with sufficient confidence to justify the imposition of controls." Second, the control problem: "by the time a technology is sufficiently well developed and diffused for its unwanted social consequences to become apparent, it is no longer easily controlled. Control may still be possible, to some degree but it has become very difficult, expensive and slow." Collingridge was concerned in relation to nuclear technology, principally with controlling technology to mitigate its adverse effects rather than to secure economic or social advantage.

[165] Although scientific research is largely thought of as orientated towards the global production of knowledge, nation states have long sought to shape the process of scientific research and technological innovation through various measures that are associated with industrial policy or 'innovation policy'. Such policies are typically formulated with the interests of the state in mind, particularly that of improving national productivity and economic growth, based on a belief that this translates into quality of life improvements for national populations. However, the capacity of states to shape technological trajectories has eroded as a result of various dynamics associated with globalisation, particularly the liberalisation of cross-border trade, yet the degree of control exerted at the national level varies between policy sectors. At the same time, the particular range of

public policy rather than of simple private morality because, by hypothesis, what one person does (or what a number of people may individually choose to do) has an effect on others with whom they share the conditions of common life, potentially on the nature and character of the society as a whole. (This is one sense in which the adoption of particular technologies can be socially transformative, although biomedical technologies are not unique in this respect.) The question of how public policy can ensure that genome editing will benefit people and societies is a much larger and inevitably much more complex one than asking whether a specific technology should be allowed or prohibited.[166] Public policy is always also informed by public morality.

2.49 The setting of public policy to reflect the public interest and promote the public good raises much debated questions of political philosophy. In these debates, questions of how freedom of individuals should be constrained by the interests of others or of the group as a whole and the prerogative of the state to assert them are all at stake. We have suggested above that certain biomedical technologies can be socially transformative, although we will have more to say about the justification for making heritable genome editing interventions the object of public policy in the next chapter. We have also implied that there are normative reasons for turning to certain sorts of democratic processes as a component of RRI, although questions of how to determine where the public interest lies on any particular issue, let alone in relation to the complex, evolving life of a polity, is another matter of infinite debate. This is, however, far from a counsel of despair. Although we must accept that it is highly unlikely that agreement will emerge from any process that does not do unacceptable violence to the views of at least some members of society, posing and re-posing questions about satisfaction with the present state of society and the kind of society it would be desirable to bring about is an indispensable orientation for public policy.[167] Though individual technologies are only a small factor, exploring visions of futures in which these technologies are in play can help to illuminate its potential for social impact, diffusion and transformation in use.[168] Envisaging how societies make systemic adaptations to different technological factors can itself help to reveal and, by revealing, even address the potential for unanticipated and unintended consequences.[169] Here, once again, the aim is to move beyond thinking about the immediate consequences of using genome editing in order to consider what a society in which such techniques were widely available would be like.

policies adopted by a state under the rubric of innovation policy varies considerably, owing to a wide range of economic, cultural, political and historical factors. See, for example: OECD (2010) *The OECD innovation strategy: getting a head start on tomorrow*, available at: http://www.oecd.org/sti/inno/theoecdinnovationstrategygettingaheadstartontomorrow.htm; Shukla-Jones A, Friedrichs S, and Winickoff, DE (2018) Gene editing in an international context: scientific, economic and social issues across sectors, in *OECD science, technology and industry working papers*, available at: https://www.oecd-ilibrary.org/industry-and-services/gene-editing-in-an-international-context_38a54acb-en.

[166] Policy questions of this kind have been described as 'wicked problems' that do not have straightforward 'right' answers. Wicked problems were first analysed as such in Rittel HJ and Webber MM (1973) Dilemmas in the general theory of planning *Policy Sciences* **4**: 155–69; see also Peters BG (2017) What is so wicked about wicked problems? A conceptual analysis and a research program *Policy and Society* **36(3)**: 385–96.

[167] Parker M (2007) Deliberative bioethics, in *Principles of health care ethics*, Ashcroft RE, Dawson A, Draper H, and McMillan JR (Editors) (Chichester: John Wiley & Sons), pp185-193.

[168] 'Socio-technical imaginaries' are collective visions of desirable futures (or of resistance to undesirable futures) animated by shared understandings of forms of social life and social order attainable through, and supportive of, advances in science and technology. They are collective, durable and capable of being performed, but also temporally situated and culturally particular. Moreover, they are at once products and instruments of the co-production of science, technology and society. See: Jasanoff S and Kim S-H (Editors) (2015) *Dreamscapes of modernity: sociotechnical imaginaries and the fabrication of power* (Chicago: University of Chicago Press).

[169] See: Merton RK (1936) The unanticipated consequences of purposive social action *American sociological review* **1(6)**: 894–904. Merton shows, in relation to Marx, that bringing a potential undesirable consequence to salience can itself result in the development of conditions to forestall it.

2.50 This raises the question of what sort of social processes might be desirable.[170] We indicated above how RRI has taken up the tools of public engagement, but this could take a range of different forms.[171] Though such processes can produce broad agreement, it is unlikely that they will generate complete consensus (whether about the significance of different outcomes, their likelihood or their desirability), which raises questions for the legitimacy of any policy informed by them.[172] While this observation conventionally focuses attention on procedural legitimacy, the persistence of unmediated dissent is a signal that the underlying questions cannot be erased once and for all and that critical reflection on the modes of engagement is itself warranted.[173]

Normative change

2.51 Given what we have said about the interpenetration of technology and society, it is inevitable that questions about the governance of biomedical technologies should be revisited as conditions change from the direction of technology, but also as social conditions change. Public moral norms can evolve (e.g. attitudes to sexual orientation) and respond to experience (e.g. norms relating to IVF and embryology).[174] These norms form a complex system of interconnected values that is woven through the 'moral fabric' of society. Changes can come from any direction: changes in statute law over time, for example, both reflect and affect such norms.

2.52 A key question for our inquiry is that of the relation between prevailing moral norms and categorical ethical standards. It is often objected that without any further constraint, societal norms can slide down a kind of 'slippery slope'.[175] Such an objection has logical and empirical forms.[176] In its logical form, the argument purports to reveal the truth of a premise that applies to distinct but related cases.[177] But it must assume that this premise is invariable. If the premise is, for example, an intuition about the wrongness of a particular act, one that might change in time and in the light of experience, then the argument might not hold.[178] Another kind of concern is that if a technology is developed

[170] It is striking that many position statements of institutions and groups that have considered reproductive uses of genome editing have concluded, apparently uncontroversially, that it should not move ahead until there is 'broad societal consensus' or agreement (e.g. statement from the organising committee of the National Academies' summit, available at: http://nationalacademies.org/gene-editing/Gene-Edit-Summit/). How the field of public debate is constituted, who is included and excluded, what processes are followed and how the outcome is understood are all complex questions. We take these up in Chapter 4 below.

[171] For a discussion of the reasons why public processes are particularly valuable in the case of biotechnologies, see: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies, chapter 5 (especially Chapter 5, 5.61ff). For their role in RRI, see: https://www.rri-tools.eu/.

[172] "I don't trust humanity. Look who we put in office for president of the US. Maybe one day when we are bit more sophisticated as a species, have dealt with our race, gender, religion, ethnicity and class issues we would be able to revisit this conversation. But not now. I think terrible things would happen… terrible terrible things" (questionnaire respondent).

[173] This set of questions will be taken up in relation to the review of the suitability of legal and other governance measures in Chapter 4.

[174] For a recent paper on normative change, see: Sunstein CR (2018) Unleashed Social research: *an international quarterly* **85**: 73–92.

[175] The argument has something like the following form: (1) accepting practice X entails accepting practice Y (where X and Y are different, but apparently innocuous uses of technology); however (2) accepting practice Y entails accepting a morally objectionable practice Z; therefore (3) accepting practice X entails accepting a morally objectionable practice Z; therefore (4) we should not accept practice X (i.e. X should be prohibited).

[176] See: Williams B (1995) Which slopes are slippery? in *Making sense of humanity and other philosophical papers 1982–1993* (Cambridge: Cambridge University Press), pp 219-20.

[177] The argument depends on the implicit premise (P) in virtue of which X, Y and Z are all evaluated. However, the argument both depends upon and proposes to demonstrate the truth of P. So, for example, if P rests on a moral intuition of some kind, we can ask whether this intuition might not be capable of alteration in response to experience.

[178] Slippery slope-type objections succeed if it can be denied that the premise, P, can change; for example, if P is some sort of universal moral principle that can be applied *directly* to X, Y and Z, so that the changing context in which each successively occurs does not matter. But in this case it is necessary both to justify this claim about the experience independence of P and

for a seemingly laudable or innocuous purpose, it will be difficult to stop it being used for further purposes that are unacceptable. This consequence is not inevitable, however, particularly if it is possible to regulate the field reliably.[179]

The global context and global public interest

2.53 Public policy concerns shaping, pursuing and avoiding complex states of affairs for a nation state within the jurisdiction of laws. Almost all nation states, however, are embedded in a global context over which they have little overall influence.[180] While the regulatory conditions for innovation are largely set nationally (or, in some cases, regionally, for common markets), researchers and innovators (just like commercial firms) who are relatively mobile can, in principle, 'shop around' for the most favourable conditions internationally. This, in turn, may encourage countries to set conditions that are attractive to the kind of researchers and innovators (and firms) they would like to attract. These may be fiscal and commercial conditions, but also potentially regulatory conditions.[181] This does not automatically imply a pressure to deregulate, resulting in an inevitable 'race to the bottom': jurisdictions with clear and stable regulation (and pathways to market) may be preferred to those without established structures for development, recognition and reward.[182] Other factors may, of course, influence the geographical displacement of resources, such as the concentration of expertise and finance and the congeniality of the destination country for researchers.

2.54 Jurisdictional thresholds uphold a mixture of social values and 'techno-nationalist' economic interests. Nevertheless, the facts that different conditions exist in other jurisdictions and that people, tissues, technologies and knowledge can pass more or less freely across national borders raise the question of how to create the right gradient or threshold for knowledge and for people.[183] Even if a procedure is prohibited locally, information and knowledge about it may flow from jurisdictions in which it can be practised. This may have several effects. One is to encourage the flow of people (researchers, service providers and prospective patients). Another is that the flow of information, particularly evidence of successful outcomes or adverse effects, may have a relaxing or a chilling effect on local social norms. We have to consider not only the possibility of technologies emerging in our own jurisdiction, but also the possible transfer of technologies developed elsewhere, which may import ethical problems along with them. There is also the possibility that moral responsibility will be diffused around the system and will not land anywhere: international divisibility and mobility of elements of a technological intervention potentially lead to 'organised irresponsibility' in which moral

to defend the claim that the concrete case Z is inconsistent with possible interpretations of the more abstract categorical P. We will consider both of these claims in the next chapter.

[179] For a more extended discussion of slippery slopes in relation to this field, see: Pattinson SD (2000) Regulating germ-line gene therapy to avoid sliding down the slippery slope *Medical Law International* **4**: 213–22.

[180] This is mainly owing to economic interdependency, which means that modern nation states have very little control over their own economies; one result of this is that political discourse often seeks to re-instantiate national distinctions in terms of values and 'identity'.

[181] An example of a fiscal incentive is the UK's 'Patent Box' scheme, which enables companies to apply a lower rate of corporation tax (10%) to profits earned from patented inventions (or inventions covered by certain other medicinal or botanic innovation rights) on which they have undertaken 'qualifying development' (thereby encouraging the concentration of development activity in the UK).

[182] An example of preference for robust regulation is some US stem cell researchers coming to the UK to benefit from clear HFEA regulation, especially after the passage of the Human Fertilisation and Embryology (Research Purposes) Regulations in 2001 (S.I. 2001 No.188) and in the funding context created by the 1995 Dickey–Wicker amendment in the US. This created opportunities in stem cell research that were taken up in Asian countries as well.

[183] The situation with regard to the movement of people and products has, of course, changed, even since the present working party was convened, owing to Brexit and the policies of other nations such as the US.

responsibility is distributed across jurisdictions and never run to ground.[184] In Chapter 4, we will return to the questions of international regulatory compatibility and the potential role of international institutions as sites of putative 'international consensus' or international negotiation.

Conclusion: agency, contingency and momentum

2.55 In anticipating the arrival of prospective technologies, three kinds of closely related concerns can be distinguished. One is that we 'sleepwalk' into a new order as a result of uncontrolled *technological momentum* that results in poorly constrained evolution and diffusion of new technologies. This is less a kind of determinism intrinsic to technology than an abdication of moral agency, perhaps as a result of a lack of information, anticipation or reflection. It may be associated with pursuing the aims of science without an adequate consideration of their broader social and moral context and implications.

2.56 A second phenomenon to distinguish is *function creep*, whereby a technology expands its repertoire of uses to encompass closely associated purposes, usually for reasons of economic efficiency. This is not necessarily a morally troubling development – it can often be beneficial – but it can be morally troubling.[185] Considering this possibility in advance may reveal underlying values and opportunities for social control before the situation gets out of hand.

2.57 A third kind of concern is that the introduction of a new technology leads us onto a *slippery slope*. In this case, we may see the danger that lies ahead, but can find no plausible reason (e.g. a rational distinction on which to base regulatory measures) or no effective means (e.g. legislative provisions) to resist the expansion into morally deplorable applications once an initial, innocuous application is conceded. In such cases, the slippery slope is often adverted to as a reason not to embark on a particular course in the first place.

2.58 Introducing a temporal dimension and an appreciation of contextual factors (including the international context), it may be the case that at least some (although perhaps not all) of the assumptions of prevailing public morality may evolve. Often, what appear to be fundamental limits may well be prudential ones, and what might matter more is whether the emergence of the new technology resembles more an orderly development or an uncontrolled slide. Thinking about genome editing as a prospective technology encourages us to take such a perspective, one that recognises that we are caught up in the process of technological and social co-evolution rather than abstracted from it. However, this largely descriptive analysis is not informative about what the content of moral judgments *ought to be* at any point within that process, nor whether there are

[184] Emblematic of this, and relevant for the present inquiry, is the 2016 case of mitochondrial donation in which Jordanian patients of a New York fertility clinic were treated in Mexico, with some of the tissue analysis conducted by a UK team (although, on the legality of the procedure carried out in Mexico, see: Palacios-González C and Medina-Arellano M de J (2017) Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case *Journal of Law and the Biosciences* **4(1)**: 50–69). The term 'organised irresponsibility' (*die organisierte Unverantwortlichkeit*) was coined by the sociologist Ulrich Beck; see: Beck U (1995) *Ecological politics in the age of risk* (Cambridge: Polity Press).

[185] The use of preimplantation screening in assisted conception may offer an example: it is a plausible conjecture that the most common indication worldwide for preimplantation screening, which was originally developed to increase the likelihood of a live birth as a result of assisted conception treatment, is now sex selection (fact-finding meeting on reproductive genetics, 23 March 2017).

categorical boundaries that should not be crossed. It is to these questions that we turn in the next chapter.

Chapter 3

Ethical considerations

Chapter 3 – Ethical considerations

Chapter overview

This chapter proposes an ethical approach that draws on the discourse of human rights to address the complex entanglement of interests, moral claims and ethical principles engaged by prospective heritable genome editing technologies. It explores ethical arguments relating to uses of genome editing in relation to three kinds of interest, those of the individuals involved, of the society in which they live and of human beings in general.

The first section, on considerations relating to the individuals directly involved (principally the prospective parents and their future offspring), takes forward the discussion of situated decision making from Chapter 1. The chapter begins by considering the kinds of claim that arise from the interests of prospective parents in certain circumstances (their desire to have a genetically related child and the information they have about the likelihood that any child they have will have a certain genetic condition). Alongside the prospective parents' interests are set considerations about the welfare of the future person. A principle is proposed to give proportionate weight to the interests of the future offspring, recognising the interdependence of the interests involved.

The second section focuses on considerations relating to others in society, i.e. those who may be collaterally affected by the use of hereditable genome editing interventions or by the adoption and diffusion of such practices, and of society as a whole. It considers how the exercise of individual interests shapes the context in which others must pursue their own interests. Consideration is given to the implications of potential shifts in moral norms (e.g. those governing the acceptability of reproductive interventions) and the consideration owed to those whose positions in society may be collaterally affected, such as those with genetic conditions that may be the target of interventions. A principle is proposed to ensure that proportionate weight is given to the interests of all, recognising the fact that individuals regulate their common life according to an integrated system of social and moral norms.

The third section focuses on considerations relating to future generations and to humanity in general. This section considers the relationship between 'the human genome' and human rights, and the nature of the alleged harms against which several international legal instruments are supposedly levelled. Although there are many suggestions in the law and in academic literature of a connection between the possession of a human genome and the enjoyment of human rights (or the possession of human dignity), such a connection does not appear necessary. The section concludes by addressing the question of directing human evolution and the possibility that genome editing may create significant inequalities or divisions among humans, or even lead to a divergence between those who have, and those who have not, been born following genome editing.

The chapter concludes that none of the considerations raised yields an ethical principle that would constitute a categorical reason to prohibit heritable genome editing interventions.

Introduction

3.1 At the conclusion of Chapter 1, we began to examine the interests at stake in the use of genome editing to influence inherited characteristics, prompted by the prospect of new technologies. At that stage, we spoke about people's goals in terms of securing certain characteristics of their offspring. Not all goals have moral significance, however. In this chapter, we consider how those goals relate to morally considerable *interests* and how these interests might entail *rights* that require others to fulfil corresponding duties. Because they involve and affect others, however, the pursuit of goals and interests and the exercise of rights all entail *responsibilities* that should be understood with equal care. Our analysis distinguishes three relevant sets of considerations. The first relate to the interests of the individuals directly involved, the second to the interests of others who may be collaterally affected and the third to the interests of human beings in general. Our aim is to show how these three sets of considerations interact to guide the moral governance of the prospective technologies we have described.[186]

3.2 Although much of the discussion will be about interests and responsibilities, the approach we take in this chapter makes use of the language and concepts of human rights. Articulating these issues in a rights discourse offers a way of relating the interests of individuals to those of the society in which they live and, potentially, to more abstract interests of humanity in general. This approach also has practical advantages. It provides widely understood language for discussing bioethical issues that is not philosophically obscure. Rights concepts also interlink readily with legal systems that potentially offer a high-level governance structure for the procedures we are discussing. Finally, given that these issues are global in scope, it is helpful that the language of human rights is internationally recognised and respected. While speaking in this register, we will nevertheless strive to capture aspects that seem intuitively important, such as the force of the desire to have a healthy, genetically related child, the experience of interpersonal relationships and how human agency is shaped and constrained by language and culture (including, of course, the language of rights).

Individuals

Respect for reproductive goals

3.3 It is important to recognise that reproductive desires are embodied in *people*; they have a force and an urgency that are *felt* as well as *reasoned*. For many people, the desire to have children is one of the most profound desires that they experience. They might think about their future child and of how their lives might change when that child is born. The image they have of the future child might not have very precise definition: a complex image that is undecided between many mutually exclusive features (sex characteristics, eye colour, etc.), but it will probably nevertheless embody certain assumptions.[187] Certain kinds of prior genetic knowledge may give prospective parents reasons to think about their future child in more particular ways. If they or a close relative have an existing child with an inherited metabolic disease, for example, prospective parents may have reason to believe that a future child of theirs may also have this disease. Genetic testing of the

[186] Our approach aims to find a way of bringing together sets of concerns that initially seem hard to relate. As a respondent to our refreshed *Call for evidence* put it: "A discussion is needed on the balance of rights of parents to have genetically related children versus the ethical challenges of altering the germ-line" (PHG Foundation).

[187] In relation to expectations about the sex of future children, see: Scully JL, Shakespeare T, and Banks S (2006) Gift not commodity? Lay people deliberating social sex selection, *Sociology of Health & Illness* **28(6)**: 749–67.

prospective parents may assign a statistical likelihood to this outcome or to a range of other heritable conditions. While their desire for a child will still be keenly felt, prospective parents in such a position may begin to think more deliberately about their reproductive options.

The desire for genetic relatedness

3.4 For many people, for whom considered decisions about childbearing are possible, the desire to have children is not simply the desire to be a parent or to form a family. It may also involve the desire to parent a child who embodies a genetic connection to them. Many women and couples who experience difficulty in becoming pregnant decide to undergo *in vitro* fertilisation (IVF) in order to have genetically related children even when other parenting options may be available. They do this despite the financial cost, physical demands and health risks involved and the uncertainty of the achieving the desired outcome.[188] The reasons for this are, however, less well examined than many other questions relating to assisted conception.[189] In this section, we review some of the many reasons that people may have for valuing genetic relatedness.

3.5 Early anthropologists started with the assumption that family (kinship) relations were the cultural representation of biological facts and that this was the same the world over.[190] Correspondingly, what were once called 'blood relationships' have been seen, in some cultures, as an important part of family (kinship) relations. Partly for this reason, people might continue to believe that the absence of such a link could have a negative impact on the children or on family relationships, or that children, parents and/or families fare better when they are genetically related to one another.[191] This normative belief is by no means universal, however. Anthropological research, including ethnographic studies of diverse cultures and of non-traditional family formation through adoption or assisted reproduction, suggests that the association between kinship and genetic relatedness is contingent and may be becoming more fluid in modern societies.[192]

3.6 In some cases, the desire for a genetically related child might express a desire of the prospective parents to reproduce something of themselves and to see this reflected in another, who will bear it beyond the limits of their own lives and secure their biological legacy.[193] In some cases, the primary desire might be to 'specify' the biological parent,

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[188] This demand is answered by the *in vitro* fertilisation (IVF) industry, which serves a UK market that, by one estimate, has been projected by grow by 7.7% annually to reach US$685.4 million by 2022. (Figures from Allied Market Research (2017) *UK IVF services market by end users (fertility clinics, hospitals, surgical centers, and clinical research institutes), and cycle type [fresh cycle (non-donor), thawed IVF cycle (non-donor), and donor egg IVF cycle] – opportunity analysis and industry forecast, 2014–2022*, available at: https://www.alliedmarketresearch.com/uk-ivf-services-market).

[189] Karin Lesnik-Oberstein has conducted work in this field. See: Lesnik-Oberstein K (2008) *On having an own child: reproductive technologies and the cultural construction of childhood* (London: Karnac Books).

[190] Edwards J (2014) Undoing kinship, in *Relatedness in assisted reproduction*, Freeman T, Graham S, Ebteha JF, and Richards M (Editors) (Cambridge: Cambridge University Press); for early 'biologistic' theories of kinship, see: Morgan LH (1871) *Systems of consanguinity and affinity of the human family*, Volume 218 (Washington, DC: Smithsonian Institution).

[191] This finding is reported in Golombok S (2015) *Modern families: parents and children in new family forms* (Cambridge: Cambridge University Press). It has been argued that while it is not wrong to adopt existing children, it is wrong to create children with the intention that they be raised be people other than their biological relatives; see: Velleman JD (2005) Family history *Philosophical Papers* **34(3):** 357–78. This argument has been strongly rejected by others, however; see: Witt C (2014) A critique of the bionormative concept of the family, in *Family-making: contemporary ethical challenges*, Baylis F and McLeod C (Editors) (Oxford: Oxford University Press).

[192] For the relative importance of socio-cultural factors, see Schneider DM (1984) *A critique of the study of kinship* (Ann Arbor: University of Michigan Press); for a cultural anthropology perspective, see: Franklin S (1997) *Embodied progress: a cultural account of assisted conception* (London: Routledge).

[193] On reproducing oneself, see: Rothman BK (2004) Motherhood under capitalism, in *Consuming motherhood*, Taylor J, Layne L, and Wozniak D (Editors) (New Brunswick: Rutgers University Press); on narcissism, see Murray TH (1996) *The worth of a child* (Berkeley: University of California Press); on confronting finitude, see: Fritsche I, Jonas E, Fischer P, *et al.* (2007) Mortality salience and the desire for offspring *Journal of Experimental Social Psychology* **43**: 753–62; on biological legacy,

rather than the desire to specify the child, where the motivation for pursuing technological solutions is to avoid involving a third-party donor in a private project. Genomics adds another layer of complexity to the understanding of interpersonal relationships, just as it does to the understanding of health and disease (see Chapter 1 above). This sets the seal on folk understandings of the inheritance of visible characteristics, while in some cases genetic inheritance is bound up with ideas of ethnicity, culture and even personality.[194]

3.7 Much of what is said about the importance of genetic relatedness is speculative, however, and where evidence from social research exists it is often inconsistent and inconclusive. People's motives can be mixed, both self-regarding and other-regarding, sometimes irrational or based on possibly false beliefs. What we can conclude is that the significance of genetic relatedness varies among people, between cultures and perhaps also over time and in response to personal experience. Among millennials in industrialised societies, its importance may be in decline.[195] Furthermore, this importance is constituted for different people and articulated by them in a large number of different ways. Although there is a variety of explanations for why people may want genetically related children, none of these is in itself a justification for a moral claim to respect and support their reproductive projects. There is a difference, in other words, between understanding *why people want* genetically related children and understanding why they *should be helped to have* them.

3.8 Below, we will consider two sorts of reason to respect and support the reproductive projects of others: the first is that there is something in the nature of these projects that calls to a value that is recognised and shared; the second is that there is a reason to support or at least not to interfere with these projects in order to protect a fundamental freedom. Before turning to this, we should note two important points: the first is that talk of 'desire for a child' situates this discourse at a particular intersection of life courses: the prospective parents' desire for a child who is not yet born. This perspective may, however, place undue emphasis on the early stages of life. Children grow up: the consequences of having a child are to bring about the existence of a person with a whole life, however long that may be, all of which, not merely the childhood part, holds value for them.[196] The second point is that people are born into relationships with others, which may persist and develop through their lives. The possibility of their identity and moral agency cannot be understood independently of these relationships, as if they first inhabited discrete universes and were then free to form strategic relationships according to their intrinsic or endogenous interests.

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see: Wisman A and Goldenberg JL (2005) From the grave to the cradle: evidence that mortality salience engenders a desire for offspring *Journal of Personality and Social Psychology* **89**: 46–61.

[194] Cooper S and Glazer ES (1998) *Choosing assisted reproduction: social, emotional & ethical considerations* (Indianapolis: Perspectives Press); Hershberger P, Klock S, and Barnes R (2007) Disclosure decisions among pregnant women who received donor oocytes: a phenomenological study *Fertility and Sterility* **87(2)**: 288–96.

[195] Professor of Philosophy, Francoise Baylis, who reviewed this report, told us: "I certainly know of many young women who announce they have no intention of having children. Interestingly there is also speculation that egg freezing fits this. Young people freeze eggs not necessarily to preserve their fertility, but to preserve their freedom so that when others comment on their childlessness they can assure them that they have eggs in storage meanwhile having no clear plan about using them." Details of the external review process can be found in Appendix 1.

[196] Caney states that the 'future generations' can be defined in three distinct ways: "those not yet born," "those not yet citizens" (which would include children currently alive) and a third conception that "for any age cohort… refers to all the age cohorts that come after it (which can include not only children but also other adult citizens, as well as the unborn)" (Caney S (2018) Justice and future generations *Annual Review of Political Science* **21**: 475–93). However, he argues that more important than the exact definition of future generations is the consideration of normative arguments about what is morally distinct about future generations and the implications this might have for identifying to whom obligations might be owed.

Procreation as a good

3.9 One view of procreation is that it is a natural expression of what it is to be human. On this 'naturalistic' view, procreation has a privileged role in what constitutes 'human flourishing', the fulfilment of an inherent end or plan. Flourishing in this way is supposed to bring happiness while its frustration entails a privation of happiness.[197] Thus, a desire for a genetically related child is seen as part of what is natural for men and women to want (and, implicitly, that not wanting children is a moral failure).[198] Some 'pronatalist' (or just 'natalist') positions see reproduction as a moral duty, and many faith groups, including some Jewish and Christian denominations, encourage procreation (as well as, in some cases, opposing contraception and abortion).[199]

3.10 Alternatively, having a genetically related child might be seen less as a fulfilment of a natural function than as the satisfaction of a natural human desire.[200] This is a view that may be particularly informed or influenced by the reported sense of incompleteness, unhappiness or lack of fulfilment by some of those who do not have the opportunity to raise children.[201] An objection to such overtly or implicitly naturalist positions, however, is that while it is empirically evident that many people have strong yearnings to have children, it is equally evident that many do not. Such an approach therefore risks leading to the unwarranted, unjust and potentially offensive conclusion that the position of such people is 'unnatural'. Rejecting naturalism, some commentators argue that the desires that women (especially) feel for children are, in fact, strongly conditioned by social and cultural expectations and, furthermore, that they are part of a structure that systematically disadvantages or oppresses women.[202]

3.11 Many social arrangements favour having children. 'Child-less' adults may be excluded from parts of shared social life and they may not benefit from economic advantages that many states make available to parents. Some states, among these Japan, Singapore and South Korea, have explored more overtly pronatalist policies, in some cases for economic reasons and in order to redress declining indigenous populations. In other cases, having genetically related children is seen as a way of maintaining distinct or threatened ethnic identities.[203] (Pronatalist policies have also infamously been adopted

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[197] The idea of 'human flourishing' is associated with the philosophy of Aristotle and its transmission through medieval Aristotelianism and the Roman Catholic Church.

[198] The position that reproducing is natural for human beings was endorsed by the US President's Council on Bioethics in Kass L (2003) *Beyond therapy: biotechnology and the pursuit of happiness* (New York: Harper Collins); social scientists Susan Cooper and Ellen Glazer also suggest that such aims are thought to be morally admirable; see: Cooper S and Glazer ES (1998) *Choosing assisted reproduction: social, emotional & ethical considerations* (Indianapolis: Perspectives Press). This often does not extend to disabled people, who are sometimes considered 'selfish' to want to have children, whether or not their impairment is heritable. The topic of whether disabled people experience discrimination when attempting to access assisted conception services was explored in the 2009 BBC radio programme *Inside the ethics committee: disability and fertility treatment* and is addressed in Mitcherson KM (2009) Disabling dreams of parenthood: the fertility industry, anti-discrimination, and parents with disabilities *Law and Inequality* **27**: 311. Discrimination against disabled people in parental custody cases is addressed in Powell R (2014) Can parents lose custody simple because they are disabled *GPSolo* **31**: 14.

[199] See, for example, the mitzvah (commandment) to "be fruitful and multiply" (*Torah*, Genesis I:28), interpreted in the Halakha (the body of Jewish religious law) as requiring at least two children where possible; see also the Catholic Church's *Code of canon law*, Book IV, Part I, Title VII, Can. 1055 §1.

[200] *Report of the Committee of Inquiry into Human Reproduction & Embryology* (the 'Warnock Report') 1984 (Cmnd 9314) (London: HMSO). In the Warnock report, it is said of those seeking assisted conception that "in addition to social pressures to have children there is, for many, a powerful urge to perpetuate their genes through a new generation. This desire cannot be assuaged by adoption."

[201] Edwards RG and Sharpe DJ (1971) Social values and research in human embryology *Nature* **231**: 87.

[202] Sherwin S (1987) Feminist ethics and *in vitro* fertilization *Canadian Journal of Philosophy*, (Supplementary Volume) **13**: 265–84.

[203] See, for example, Kassel R and Dorff E (2007) *Mitzvah children responsum of the Committee on Jewish Law and Standards of the Rabbinical Assembly*, available at: https://www.rabbinicalassembly.org/sites/default/files/public/halakhah/teshuvot/20052010/mitzvah_children.pdf. "In the past, the challenge to Jewish survival was a result of persecution. Today the challenge is one of seduction into the general, secular culture through assimilation, intermarriage, and a commitment to work over family."

for nationalist and racist reasons, forging identities at a biological, social and political level.) In more industrialised economies, pronatalism tends to be tempered by more cosmopolitan concerns about global overpopulation and the exacerbation of poverty and social inequality.

3.12 While it is clear that many people desire to have genetically related children, it is hard to demonstrate that having genetically related children, or even having children at all, is a good in itself. This may be beside the point, however. In spite of attempts to demonstrate both that people should and should not have children – or have/not have them in certain circumstances – the complex motivations that people express seem rarely to be governed (or governable) by theoretical rationality.[204] We may nevertheless have good reasons to respect them, and those reasons may not be that they are good desires, but that they are the desires of people for whom we should, *a priori*, have respect. We explore this argument in the next section before considering whether, if it holds, there are moral reasons to place limitations on the expression of those desires.

Respect for procreative interests

3.13 Focusing on the freedom to pursue procreative interests independently of the moral value attached to the goal has the intuitive appeal of not automatically putting people who have no particular desire for genetically related children – or any children at all – outside the norm. More generally, where people who have different personal value systems inhabit a common social world, this allows us to bracket (for now) arguments over the relative moral value of different goals and to approach our problem through a different set of questions; namely, questions about when it is morally permitted (or required) to interfere with (or to assist with) their projects.

3.14 As a negative right, the putative right to procreative freedom may be thought of as a special kind of privacy right, a right to control one's own body and not to be impeded or interfered with by others in a way that obstructs the pursuit of one's freely chosen goals.[205] It says nothing special about reproduction other than to single it out for this kind of protection. But if the interest in having a child were a normatively important one, it might be thought to entail a positive right that goes beyond the right to non-interference. In practice, this might generate an entitlement to assistance, such as funded access to assisted conception services (although not only biomedical technologies, but also a variety of forms of assistance for family making). Some authors have indeed made the case for such a positive right, either as a stand-alone right or to redress underlying inequality.[206] Even if such a right could be established, however, the existence of a corresponding obligation is likely to depend very much on the social context: on the availability of safe and effective technology, for example, and on the absence of overwhelming opportunity costs for health services if they are to be funded publicly.

3.15 There is therefore an asymmetry between the negative right – the right to be 'let alone' – and any positive entitlement to assistance. The enjoyment of the negative right is not

[204] See, for example, Häyry's various arguments against procreation and responses to these: Häyry M (2004) A rational cure for prereproductive stress syndrome *Journal of Medical Ethics* **30**: 377–8; Häyry M (2004) If you must make babies, then at least make the best babies you can*? Human Fertility* **7**: 105–12; Takala T, Herissone-Kelly P, and Holm S (Editors) (2009) *Cutting through the surface: philosophical approaches to bioethics* (Amsterdam: Rodopi); on the absurdity of reproduction see: Ashcroft R (2009) Is it irrational to have children? in the same volume.

[205] On reproductive autonomy as a negative right, see: Dworkin R (1993) *Life's dominion: an argument about abortion, euthanasia, and individual freedom* (New York: Alfred A. Knopf). For more on negative rights, see: Narveson J (2001) *The libertarian idea* (Ontario: Broadview Press).

[206] See: Mills C (2011) *Futures of reproduction: bioethics and biopolitics* (Dordrecht: Springer).

dependent on the content of the interest that it guarantees can be expressed (albeit that it may be qualified on account of its effects on others). It is perfectly consistent to respect a desire that one does not or cannot share. The positive claim, on the other hand, seems to depend very much on the involvement of others and therefore on the content of the desire being normatively endorsed, for which other supporting reasons may be required, particularly if it is a desire that is not universally shared.

A constraint on the pursuit of reproductive interests

3.16 Rights offer a way of structuring relations between people whose interests potentially interfere with each other. If fundamental rights are to be held equally by all people, they must be capable of reasonable qualification where there is a possibility that one right holder exercising their right can interfere with another's interests that are similarly protected by a right.[207] This interference may be direct (effect on another individual) or indirect (effect on the conditions of common life that negatively affect others). Human interactions are, however, for the most part beneficial: as we noted above, people are born into a world of relationships with others, and the possibility of fulfilling of their interests largely depends on their relationships with others and their compatible and congruent interests. In cases of human reproduction, the person most directly affected by the fulfilment of the prospective parents' reproductive interests – namely their prospective offspring – does not exist. In this section, we will explore how consideration of the interests of future people is morally warranted and what its implications might be for the reproductive interests of prospective parents.

The interests of the future person

3.17 It appears, intuitively, that some decisions that prospective parents may make in the light of the genetic knowledge available to them may affect the interests of their future child.[208] In the case of a serious inherited metabolic disorder, as discussed above, the prospective parents might decide to use a preimplantation intervention to secure that an embryo to be transferred is not affected by that disorder. In this case, if the transferred embryo results in the birth of a child, that child will not have the disorder. The prospective parents might, on the other hand, decide to conceive without assistance. In this case, there is a chance that their child will be affected by the disorder. These two possible children would probably have very different lives. We can also imagine a variation of the first of these two cases (preimplantation intervention) in which the child was not affected by the condition, but their developmental potential was somehow restricted as a consequence of the procedure itself, in a way that did not come to light until after the birth. The decisions of the prospective parents to take one approach rather than another can have significantly different consequences. But how, if at all, does the anticipation of these consequences matter?

3.18 The moral permissibility of reproductive decisions is philosophically complex and an area of contested argument. The two problems that beset these discussions are whether it is possible to say any kind of life is worse than not existing and whether we can say that creating a life which is worse than some other we could have created is harming or wronging the person we do create. While some philosophers hold that existence is itself

[207] While conflicts between legal rights are common currency in legal proceedings, some philosophers think that there can be no conflict between genuine rights because, for example, a condition on a set of rights being just is that they are at least mutually consistent; see: Steiner H (1994) *An essay on rights.* (Oxford: Wiley Blackwell).

[208] Here, we assume that while the desire to have a child may be irrational, the choice of means is a more reflective decision – see Chapter 1.

a benefit, so long as the life that exists is not so bad as to be not worth living, others argue that it is always better not to have been born.[209] But unless being brought into existence is itself a harm, it can seem difficult to argue that any life-giving reproductive decision can be wrong, at least on grounds relating to the welfare of the future person whose existence is a consequence of it. The fact that this conflicts with our intuition that some of the decisions that prospective parents make about having children matter morally is the nub of an issue known to philosophers as the non-identity problem.[210]

Box 3.1: The non-identity problem

In *Reasons and persons*, the philosopher Derek Parfit invites his reader to imagine trying to persuade a young girl not to have a child now, because that child will have a poor quality of life, but to have a child later instead, one who will have a better quality of life. The girl is entitled to reject the argument that it is in *her own* interest to delay conception because she has a right to do what is not in her best interest. When appeal is made instead to *her child's* interest it is argued that in neither case (conception now or conception later) is any child harmed: in both cases her child would have a life worth living and in neither case can that child swap the life they have for the life of the other, since they are numerically distinct (*non-identical*) children. Neither outcome appears to be better or worse than the other because there is no one for whom it is better or worse.

The non-identity problem has been applied to a variety of assisted conception examples, including selecting between embryos using preimplantation genetic testing and preferring different approaches to mitochondrial donation.[211]

3.19 A problem of much philosophical argument in this area, as in others, is that argument leads us to endorse conclusions or judgments that clash with our intuitions. It is a further matter of philosophical argument as to whether we should revise our intuitions or reject our conclusions. Either is thought to be problematic. Although we do not propose to engage here in a long discussion of a problem that has, after all, taken up many full-length books of philosophy and still resisted solution, we should not dismiss the non-identity problem simply because it can seem very removed from everyday concerns about reproductive decision making or because we have decided to talk about rights rather than consequences. Consequences matter, not least because deliberate reproductive decisions are guided by the goal of bringing about one state of affairs rather than another. The difficulty we have is that of bringing the interests of future people into

[209] The first position is discussed in Parfit D (1987) *Reasons and persons* (Oxford: Clarendon Press). The contrary ('antinatalist') position is argued in Benatar D (2008) *Better never to have been born: the harm of coming into existence* (Oxford: Oxford University Press). St Augustine (along with the majority of the Church fathers) argues that marriage is good, though celibacy is better and virginity best; indeed, he does not appear to think that the perpetuation of the human species is a good in itself; see: Augustine, *De bono coniugali*, 10. David Benatar defends the view that being brought into existence is always a harm and that it is always wrong to have children and, furthermore, that it would be better if humanity became extinct.

[210] See Parfit D (1987) *Reasons and persons* (Oxford: Clarendon Press). Boonin, in a book-length survey of the problem and related scholarship, argues that we should accept the conclusion that neither choice – for the girl in Parfit's example to conceive now or conceive later – is wrong; see, Boonin D (2014) *The non-identity problem and the ethics of future people* (New York: Oxford University Press).

[211] Harris has used it widely and often in his work. Recently, the problem has been discussed in relation to mitochondrial donation by Wrigley, Wilkinson and Appleby, who argue that pronuclear transfer is a morally preferable technique to maternal spindle transfer due to the non-identity problem (Wrigley A, Wilkinson S, and Appleby JB (2015) Mitochondrial replacement: ethics and identity *Bioethics* **29(9)**: 631–8); this is rejected by Rulli, who adopts the reproductive framing against the therapeutic framing for both cases (see: Rulli T (2017) The mitochondrial replacement 'therapy' myth *Bioethics* **31**: 368–74).

play in the evaluation of decisions on which their existence, and therefore their capacity to have interests or rights at all, depends.

3.20 In the example we gave above of the prospective parents whose child would have a likelihood of inheriting a serious metabolic disorder, there was a noticeable slippage between referring to the 'future child' and the 'two possible children'.[212] This slippage involved a shift of mental orientation towards the imagined offspring that corresponds to imagined perspectives from before and after different processes of conception, pregnancy and birth. This is important. In each case, the offspring we are discussing are not real, independently existing people, but mental images. We suggested above that, before having a child, prospective parents may have a mental image of their future child. If a pregnancy occurs by accident, the prospective parents might not begin to form this image until they know that the pregnancy is in progress. If they are planning to conceive a child, they may have an image of what they imagine that child will be like that is informed by common assumptions drawn from wider experience. If they know, through genetic testing, that there is a likelihood of their child inheriting a specific genetic condition, that condition may be part of the image. The concept of the 'future child' is accommodating two contradictory images, things that cannot exist together in reality (e.g. different sex characteristics, blue eyes and brown eyes).[213]

3.21 As successive decisions are made (some deliberate choices, others not), the contradictions that are possible in the concept of the 'the future child' become progressively resolved. The options available will depend greatly on people's circumstances – in many parts of the world, the chance of inheriting characteristics present in the biological family may not be confirmed by genetic testing and options may be limited to choice of reproductive partners. For the couple who wish to act on prior genetic knowledge of what characteristics their child might inherit, the first decision is perhaps whether their 'future child' will be genetically related to both or to either of them. (If not, then the same questions arise again, but with a different set of possible genetic endowments, such as those of a gamete donor or of other people). Though this narrows the range of possibilities, the 'future child' still has many other possible forms, which it makes sense to think of as being associated with, among other differences, different levels of welfare. As they move through decisions about the procedure, timing and conditions of reproduction, the concept of the 'future child' becomes progressively more closely identified with an actual child who will have been born as a result of a particular combination of gametes, in particular circumstances, at a particular time.[214] At the point at which a pregnancy begins, there may still be many things that the prospective parents do not know about the future child they expect to have.[215] Some of the things they may know, however, are genetic characteristics that they have deliberately selected or deselected.

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[212] We said first that "some decisions that prospective parents may make in the light of the genetic knowledge available to them may affect the interests of their future child," and then that "These two possible children would probably have very different lives" (paragraph 3.17 above).

[213] The philosopher Gottfried Leibniz described things that cannot exist together as 'incompossible'. No possible world can contain things that are not compossible.

[214] It is a peculiarity of assisted conception that the 'future child' may be identified with one of a number of synchronically produced embryos, just as in the case of unassisted conception it might be identified with one of a number of eggs fertilised *in vivo* diachronically (if, for example, the first attempts at conception founder). For simplicity, we will not discuss multiple embryo transfers, but the discussion can be extended to 'future children' where multiple embryos are transferred.

[215] They may not know the future child's sex characteristics, for example, although these things will already be settled. Other characteristics will not be established until sometime during the pregnancy and, of course, many more characteristics, including epigenetic characteristics, may depend on events that happen after the child is born and throughout their life.

3.22 Thinking about reproductive decisions in terms of how they help to bring about the existence of a future child from among a number of possible (but incompossible) future children helps to bring the interests of the future child into play in reproductive decisions.[216] It reveals how these decisions, including the decision to conceive now or later, to use these gametes or others, to edit the embryos or not to do so, to select this embryo or that one, to continue or to terminate a pregnancy, all select futures in which people with particular sets of characteristics, capacities and opportunities exist rather than alternative futures in which they do not. When we say that a decision matters morally, one of the things we mean is that the person who makes the decision bears the responsibility for bringing about a state of affairs that results from that decision rather than a state of affairs that they could have brought about by deciding differently (or by not deciding when they had the opportunity to do so). Responsibility is not a discrete judgment, but a state that endures along with the consequences of the decision and underpins the real relationship that parents have with their children. Clearly, parents cannot be responsible for every aspect of their offspring's welfare, and the manner of reproduction is only one factor in this. In the next section, we consider the extent and limits of this responsibility and any moral duties associated with it.[217]

Arguments that no editing is permissible

3.23 The potential of genome editing to select certain characteristics of future people could be a power of great consequence. However, there may be many uncertainties that it cannot resolve. A source of uncertainty is the complexity of the series of consequences that follow, which make it very difficult to make assumptions about what an alternative life would have been like. A feature such as genetic relatedness or having certain other genetic characteristics is distinguishable but perhaps not separable from the psychological and social identity of the resulting person.

3.24 The imponderability of alternative possible lives might be taken as an argument for the absurdity of making any particular intervention (so long as it did not result in a 'life not worth living'). A contrary view would hold that the significance of such decisions is such that they amount to a violation of the rights of the offspring to form their own identities. Choosing someone else's genetic endowment (other than probabilistically, through the choice of a reproductive partner) might be analogous to a kind of enslavement, except that the limitations on their freedom take the form of a biological characteristic rather than a physical constraint or psychological oppression. On such a view, the intervention offends against the essential dignity and nature of the person as a free and independent human being.

3.25 One kind of objection sees that any interference with what is given is wrong because what is given is given by God or by Nature. Even without a metaphysical underpinning, other kinds of unease about the applications of life science and biotechnologies are often

[216] The 'future child', in this construction, is what is known as a *prolepsis* (the representation of a future state of affairs in the present). See also: Parfit D (2017) Future people, the non-identity problem, and person-affecting principles *Philosophy & Public Affairs* **45(2)**: 118–57.

[217] Some scholars decline to approach the problem in terms of consequences and instead focus attention on the duties prospective parents have to their offspring (e.g. guaranteeing them the prospect of a minimal quality of life); see, for example: O'Neill O (1979) Begetting, bearing, and rearing, in *Having children: philosophical and legal reflections on parenthood*, O'Neill O and Ruddick W (Editors) (New York: Oxford University Press); Feinberg J (1986) Wrongful life and the counterfactual element in harming *Social Philosophy and Policy* **4(1)**: 145; see also: Kumar R (2003) Who can be wronged? *Philosophy & Public Affairs* **31**: 99–118; Archard D (2004) Wrongful life *Philosophy* **79**: 403–20.

articulated in this way.[218] The view that 'tried and tested' natural processes are more reliable than 'human tinkering' has a powerful influence in folk morality and attitudes to risk and uncertainty.[219]

3.26 The philosopher Jürgen Habermas has sought philosophical rather than religious or prudential grounds for the preference for nature over design in "the connection between the contingency of a life's beginning that is not at our disposal and the freedom to give one's life an ethical shape." Habermas's focus is not on the external constraints on freedom of action, but on the experience of self-identity, specifically the effect that the knowledge that a person's characteristics have been prenatally determined by another may have on their understanding of themselves as an autonomous and equal member of a community of free and equal persons. He explains:

> "*In this sense, the potential harm lies not at the level of deprivation of the rights of a legal person, but rather in the uncertain status of a person as a bearer of potential rights. With the realization of the noncontingency of her manufactured biological origins, the young person risks losing a mental presupposition for assuming a status necessary for her, as a legal person, to actually enjoy equal civil rights."*[220]

3.27 To construe the ontological conditions of moral entitlement in this way is to attribute a great deal of significance to the role of the genome for a person's moral status and psychosocial identity, bordering on genetic determinism, or to show the risk of it being construed in this way. It is also exceptionalist in the sense that it treats genetic factors as radically more important than other constraints that parents might apply. (We will return to this issue below when we discuss difficulties of distinguishing acceptable and unacceptable interventions.) Nevertheless, the prospect of viable genome editing technologies requires us to confront decisions that, in 2002, Habermas might have hoped to avoid.[221] As he foresaw, the development of scientific knowledge and its diffusion in society can lead to normative shifts, potentially turning acts into omissions: when more is known about the involvement of genetic factors in observable characteristics, when it becomes normal to have self-knowledge of this kind and when, furthermore, it becomes possible to act on this knowledge for one's offspring, a shift takes place in the nature of moral responsibility. (We will return to this below when we discuss social norms in the second part of this chapter.)

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[218] Bostrom N and Sandberg A (2008) The wisdom of nature: an evolutionary heuristic for human enhancement, in *Human enhancement*, Savulescu J and Bostrom N (Editors) (Oxford: Oxford University Press). See also Nuffield Council on Bioethics (2015) *Ideas about naturalness in public and political debates about science, technology and medicine: analysis paper*, available at: http://nuffieldbioethics.org/wp-content/uploads/Naturalness-analysis-paper.pdf. A number of writers challenge the view of nature as being 'the apotheosis of engineering excellence'; see: Tooby J and Cosmides L (2010) The evolutionary psychology of the emotions and their relationship to internal regulatory variables, in *Handbook of emotions*, Lewis M and Haviland Jones JM (Editors) (New York: The Guildford Press); see also: Buchanan A (2011) *Better than human: the promise and perils of enhancing ourselves* (New York: Oxford University Press). In any case, it has been argued that nature does not always work to the advantage of individuals, and when it does, it perhaps does so only coincidentally to the propagation of genes; see Wilson EO (1975) *Sociobiology: the new synthesis* (Cambridge, MA: Harvard University Press).

[219] Coyle F and Fairweather J (2005) Space, time and nature: exploring the public reception of biotechnology in New Zealand *Public Understanding of Science* **14(2)**: 143–61.

[220] Habermas J (2003) *The future of human nature* (Cambridge: Polity). Habermas is writing primarily in response to preimplantation genetic diagnosis (and embryo research), although his argument that genetic selection involves "exercising a kind of control… that intervenes in the somatic bases of another person's spontaneous relation-to-self and ethical freedom" applies equally to genome editing, or perhaps more so.

[221] See the 'Postscript' to *The future of human nature* (written in 2002), where Habermas contrasts the German and US approaches.

Arguments that some (but not all) editing is permissible

3.28 Whereas Habermas offers reasons to refuse technological advances, other philosophers confront them as realities to be controlled. The political philosopher, Michael Sandel, argues that parents' imposition of their preferred characteristics on their offspring 'disfigures' the relation between parent and child.[222] His criticism, however, is reserved for attempts to 'enhance' the characteristics of the future person.[223] He does not criticise genetic interventions that are intended to exclude inherited diseases. The reason that excluding disease characteristics is exempt from criticism is that it allegedly promotes human flourishing, which disease inhibits. In this, he follows the US legal philosopher, Joel Feinberg, who argues that children have 'anticipatory autonomy rights' or 'rights in trust' that require the maximisation of their chances of self-fulfilment.[224]

3.29 A view that seeks to distinguish between some genetic interventions as being acceptable and others as not must, however, confront at least three sorts of difficulty. The first sort of difficulty is to justify the implicit normativity embodied in the concept of openness or flourishing. The second difficulty is finding an operationally effective way of distinguishing the class of morally permissible cases from those that should be permitted and those that should not, so as to make it possible to regulate. A third difficulty (which we have already alluded to above) is to make the case that there is something exceptional about genetic manipulations as compared to other possible interventions that prospective parents may make, both before and after conception (e.g. choices about the child's education), so as to justify treating these distinctly. We discuss these, in turn, in the following paragraphs.

3.30 ***Justifying normativity***. Whereas securing the openness of a child's future options may seem like an *a priori* good, the steps that may actually be taken require a more specific kind of justification. As a general concept, openness in fact raises a number of difficulties. A salient feature of the kind of decisions taken at the preimplantation level is that they constitute an irreversible bifurcation between future possibilities, but one that constitutes the uniqueness of their experiences. Critiques from disability rights and feminist perspectives argue that openness of one kind may well involve closure of another. Some writers argue strongly that many people's assumptions about the quality of life of disabled people are misplaced and that, in at least some cases, disability can involve freedoms that are equally valuable, albeit different to those enjoyed by others.[225]

3.31 There is undoubtedly scope for dispute about the value of the lived experience of some forms of disability, and terms such as 'harm', 'disability' and 'disease' are notoriously contested descriptions.[226] Though few would argue that disability is not a harm, in that it

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[222] Sandel M (2009) *The case against perfection* (Cambridge, MA: Harvard University Press).

[223] ibid. This echoes the view taken in a 2003 report of the US President's Council on Bioethics (of which Sandel was a member): Kass L (2003) *Beyond therapy: biotechnology and the pursuit of happiness* (New York: Harper Collins).

[224] Feinberg J (1980) The child's right to an open future, in *Whose child? Children's rights, parental authority and state power*, Aiken W and Lafollette H (Editors) (Lanham, MD: Rowman and Littlefield). See also: Davis DS (1997) Genetic dilemmas and the child's right to an open future *Hastings Center Report* **27**: 7–15. See our earlier report on mitochondrial donation, in which the consideration of the child's right to an open future was discussed and taken up, although not explicitly advocated (Nuffield Council on Bioethics (2012) *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).

[225] See, for example: Johnson HM (2005) *Too late to die young: nearly true tales from a life* (New York: Henry Holt and Co.); see also: Garland-Thomson R (2012) The case for conserving disability *Journal of Bioethical Inquiry* **9(3)**: 339–55.

[226] For this reason, the UN Convention on the Rights of Persons with Disabilities deliberately does not offer to define disability; instead, it acknowledges that "disability is an evolving concept" and takes the approach that "disability results from the interaction between persons with impairments some decisions that prospective parents may make in the light of the genetic."

entails experiences of suffering and disadvantage, many disability scholars argue that in many (though certainly not all) cases we are looking in the wrong place for the source of the suffering and disadvantage. The British social model of disability, devised by several prominent disability activists and academics in the late 1970s and early 1980s, attempts to separate impairment and disablement. On this model, an impairment is a long-term limitation of a person's physical, intellectual, psychological or sensory function, but impairments need not be disabling: disablement occurs as a result of environmental barriers, societal attitudes, etc., that exclude, oppress or disadvantage people with impairments.[227] Of course, it would be absurd to say that the removal of disabling barriers removes the harm, and in very many cases, including most inherited genetic conditions, barriers are largely irrelevant.[228] The value of the social model, though, is to prevent the collapse of a huge range of genetically related bodily differences into a uselessly homogenised concept of 'disability' and to encourage more nuanced and sophisticated analysis. (It is important to distinguish, for example, the harm of severe lysosomal storage diseases from the harm of sensory impairment or moderate learning disability.) While these considerations are important for many people or in certain circumstances, care must be taken not to overstate their general significance. In the present context, they draw attention to the importance of not ignoring context when certain states of being are defined as pathological and marked out for distinct kinds of treatment.[229]

3.32 If it is difficult to specify the boundaries of 'normal' or 'desirable' in terms of functions or capacities, to offer to do so in terms of the genome is close to absurd.[230] Human genomes exhibit a vast number of variations. In terms of range, for example, the limits are indistinct, and we have already shown how contested they can be at the margins. (Does a normal range, for example, include variations associated with marginal disease or disability characteristics, particularly where they are expressed differently in different people and may be associated with pleiotropic effects?) In terms of distribution, it is open to dispute as to what level of prevalence should mark out an allele as occurring normally, and this is further complicated by how the population in which that prevalence is measured is delimited. (For example, a certain characteristic may be a relatively common occurrence in parts of East Anglia but not in the UK population as a whole, or in parts of East Africa but not the African continental population as a whole.) Despite the reverence given to 'the human genome' in international declarations, the concept is, as we argued in Chapter 1, metaphysically incoherent. It might be superficially appealing to suggest that there is a significant distinction to be drawn between, on the one hand, editing a preimplantation genome to introduce one of a library of 'wild-type' genetic variations found in existing human populations (or the relevant subpopulation, however that may be defined) and, on the other, introducing a novel variation (perhaps one found in another species and thought to be translatable to humans). To do this, however, envisages the

[227] In the classic example, being paralysed is a physical impairment, while a lack of accessible toilets or lifts in the built environment or an employer who thinks wheelchair users are a fire hazard, is disabling. Oliver M (1996) *Understanding disability: from theory to practice* (London: Palgrave); Oliver M (2013) The social model of disability: 30 years on *Disability and Society*, 2013, **28(7)**: 1024-1026

[228] For a discussion of the social model, see Shakespeare (2010) The social model of disability, in *The Disability Studies Reader*, Davis LJ (Editor) (London: Routledge), pp 214-21.

[229] There may be people who would choose not to receive a safe and effective treatment for such conditions, should one be available. This might be for reasons to do with the burden of treatment itself or because they could not envisage making a different kind of life. And undoubtedly disease may be associated with positive experiences (of care and compassion of others, of solidarity and mutual support, etc.). They would be unlikely to argue, however, that no one in a similar position should have access to such a treatment, unless on grounds of equity and resource allocation and so long as it did not impact adversely on others (we discuss this latter implication in the second major division of the present chapter). To do so would be simply to deny the experience of morbidity for which there is ample evidence in the patient population.

[230] Sometimes, restorative interventions (like wheelchair provision) exceed the norm; see, for example: Silvers A (1998) A fatal attraction to normalizing: treating disabilities as deviations from 'species-typical' functioning, in *Enhancing human traits: ethical and social implications*, Parens E (Editor) (Washington, DC: Georgetown University Press).

human genome as a frozen and bounded concept, whereas we know it to be evolutionarily promiscuous.[231]

3.33 ***Distinguishing permissible and impermissible interventions***. If it is accepted that some capacity-increasing interventions are morally permissible, the difficulty then arises of distinguishing those from others that are impermissible. If it is to support some form of external regulation, this distinction needs to be clear, stable and well understood. In the case of preimplantation genetic testing (PGT) and embryo selection, this difficulty has been discussed in terms of distinguishing 'therapeutic' interventions from 'enhancement' interventions. One way in which such a distinction might matter is that these categories are already treated as coinciding with different sorts of moral and legal entitlement: healthcare treatments might be owed to people by states, healthcare professionals or insurers as a basic social good, whereas enhancements are pursued privately, for personal advantage. One of the factors that complicates this distinction is preventative medicine: it is not clear that an intervention that averts an outcome that may or may not have happened without it fits comfortably within this binary model, although it is an increasingly important part of public health initiatives. A second factor, as we discussed above, is that the judgment is dependent on many contextual factors, including the nature of the environment and the availability and effectiveness of different kinds of biomedical and social technologies. Given the substantial 'grey area' between these two classes, this distinction is neither clear nor well understood, and it might also be unstable.[232]

3.34 As we argued in Chapter 1, however, we have to take care when applying categories such as 'therapy' and 'enhancement' (and also prevention) to the anticipation of people who do not yet (and may never) exist. What we are talking about is bringing about people with these characteristics, not changing the characteristics of people who already exist. The fact that they will exist at all may, in fact, depend on whether the intervention is permitted. Unlike a simple medical model, where a patient, who is affected by disease, is treated to remove the disease symptoms, in the reproductive context, the nature of the moral claims and responsibilities involved is much more complex. In any case, the question of whether a given intervention constitutes therapy or enhancement (or something else), and their moral permissibility, can be debated independently of an ethical judgment about the intervention in a given set of circumstances.[233] Below, we develop an alternative approach based on individual welfare and socially normative considerations. First, however, we will discuss a third difficulty in differentiating ethically between interventions.

3.35 ***Genomic exceptionalism***. A third difficulty involved in making ethical distinctions in relation to genome interventions is finding an ethical basis on which to distinguish those interventions from other kinds of possible intervention. Why would genome interventions

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[231] This reflection raises a further question about the significance of the distinction between 'natural' and directed evolution that returns us to our starting point in the preference for nature over design (above). Indeed, the argument has been made that the real significance of heritable genetic modification may not be its capacity to exclude genetic disease characteristics, but its ability to adapt future generations to environmental change, which is happening at a rate with which 'natural' evolution cannot keep step. See, for example: Baylis F and Robert JS (2005) Radical rupture: exploring biological sequelae of volitional inheritable genetic modification, in *The ethics of inheritable genetic modification: a dividing line?* Rasko JEJ, O'Sullivan GM, and Ankeny RA (Editors) (Cambridge: Cambridge University Press).

[232] For example, the case of intervening to create genetic resistance, in people in whom it is not naturally occurring, to a serious endemic disease. (This example was presented in our public questionnaire.)

[233] Medical lawyer and ethicist, Rosamund Scott, has argued that "although we can note the lack of a clear-cut distinction between 'treatment' and 'enhancement' on a nonperson-affecting perspective in itself, we can still look beyond such an approach to other reasons for or against selecting in certain ways." Scott R (2007) Why parents have no duty to select 'the best' children *Clinical Ethics* **2**: 149–54.

be exceptional when compared to the many other ways that parents intervene in their offspring's lives, ways that also become inescapable features of their biography and conditions of their future development?[234] A reason that may be offered is that the results of genome interventions are inscribed indelibly into the biology of the future person. However, in all or even most cases, their effect need not be of greater magnitude than interventions such as physical training, educational approach, inculcating moral conscience, etc.[235] Furthermore, given the variation in expression in different people and different circumstances, genomic interventions may not be any more effective than other controls except in some highly unusual cases. In many cases, proposed genomic interventions may represent technological solutionism, displacing more appropriate and effective social responses. The means may matter as moral issues in their own right, independently of their effects or the ends at which interventions are aimed.[236]

Arguments that some genome editing is required

3.36 If the interests of future people carry moral weight we might ask whether certain genomic interventions might be morally required. The utilitarian bioethicist, Julian Savulescu, for example, has argued for a 'principle of procreative beneficence'.[237] By this line of argument, we should in fact do all we can to maximise the welfare of future people, including, where feasible, by extending or enlarging their inherited capacities. In this way, one can see how, all other things being equal, moderate injunctions should give way to seemingly more extreme ones, assuming that any contingent technical obstacles can be progressively overcome. This may raise concerns about the approach in practice.[238]

3.37 Setting aside, for the moment, considerations of social justice (to which we return in the second division of this chapter), a simple welfare maximisation criterion presents its own problems. In the first place, if this is understood as maximising a value for the future person, it is a substantial challenge to know (or to predict with any reliability) what characteristics (or even what kinds of characteristic) will be welfare promoting. The absence of some clinically treated diseases may be a strong candidate, whereas the value of other characteristics may be more arbitrary or highly context dependent.[239] Furthermore, there is a risk that, in selecting any of these characteristics, the prospective parents actually reduce their offspring's freedom by placing on them the additional burden of expectation.[240]

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[234] This exceptionalism is entrenched in certain institutional practices (such as those of US health insurers), possibly because dealing in terms of assays and alleles seems more declarative than the messy, complex and nuanced social models; see, for example: Buchanan A, Brock D, Daniels N, *et al.(*2000) *From chance to choice: genetics and justice* (Oxford: Oxford University Press).

[235] Current research is exploring the possible effects of diet (among other things) on the epigenome and also the possibility that such epigenomic changes (epimutations) can be inherited. See, for example: Heijmans BT, Tobi EW, Stein AD, *et al.* (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans *Proceedings of the National Academy of Sciences* **105**: 17046–9; Patel V and Preedy V (2018) *Handbook of nutrition, diet and epigenetics*, available at: https://link.springer.com/referencework/10.1007%2F978-3-319-31143-2.

[236] Baylis F and Robert JS (2004) The inevitability of genetic enhancement technologies *Bioethics* **18**: 1–26.

[237] Savulescu J (2001) Procreative beneficence: why we should select the best children, *Bioethics* **15(5–6)**:413–26.

[238] If one does not object to such developments in principle, one might nevertheless (as is often the case with utilitarian arguments) wish to add a principle of distributive justice; for example, that the gain in capacity for one must be conditional upon the opportunity to achieve a like increase for all and not tend to increase social inequality – see the second division of the present chapter.

[239] For example, is it an advantage to carry one copy of the sickle cell trait? Perhaps not for a person with Afro-Caribbean heritage living in a close-knit Afro-Caribbean community in London. Is it an advantage or a burden to be predisposed to risk-taking behaviour, (supposedly) as are so many company CEOs and fatally injured rock climbers?

[240] Parker M (2010) An ordinary chance of a desirable existence, in *Procreation and parenthood: the ethics of bearing and rearing children*, Archard D and Benatar D (Editors) (Oxford: Oxford University Press).

Protecting or promoting the welfare of the future person

3.38 The considerations above have helped to clarify the sorts of considerations that inform both intuitive and more reflective responses to the question of genomic interventions. From them we can derive some precepts to help guide our approach. Firstly, we have to accept that our moral decisions are made within a given social and technological context, however much we may wish the world were other than it is. This means that we have to take responsibility for both acts and conscious omissions: deciding not to use an available technology and whether to discover knowledge about the genome or to intervene in it may still count as choices that engage moral responsibility.[241] While genomic interventions of the sort discussed are not yet available, some agency is already involved in shaping the pathways of technological development; it is, in any case, surely wistfulness to imagine that, at a global level, developments now in train can be brought to a halt or turned back. Secondly, we have to understand the personal situation in which a moral decision occurs. It takes place in the context of a reproductive project of a couple who may wish to intervene in order to establish certain conditions for the life of their future offspring. It also engages the responsibilities of those who may assist them, and of the society that, through its laws and regulations (or lack of them), permits or forbids those people to assist them. The context of other rejected options is important to the understanding of the role that the option of genome editing plays in relation to their freedoms and interests. So also is the special value that is implicitly attached by those people and by society to the satisfaction of procreative desires. Thirdly, what is at stake are interventions that, along with a number of other factors, have consequences for the kind of life the future person may have. At the margin (e.g. in the case of serious inherited genetic disease), they can be strongly determinative, but genomic intervention is only one – and probably not the most significant – of the decisions that parents will make that affect their offspring (and it may become progressively less important as other biographical factors intervene, especially to the developing sense of self-identity).[242] Fourthly, given the complexity of the relationships between genetic variation, phenotype, biography and culture, it seems clear that the focus of our reflection should not be just on the genetic interventions (because genetic variation is ultimately meaningful only in the context of an embodied genome of a person embedded in a family, society and culture). We cannot predict, but we have to imagine what the lives of future people will be like and the significance of the possible interventions we might make for their embodied identities and welfare.

3.39 As we said at the start of this section, practical moral reasoning is informed by our reasonable expectations about the future. These expectations form around the mental concept of the 'future person' who is brought into present reasoning as a heuristic. They are informed (but also limited) by, among other things, understanding of the world as it is, the current state of scientific knowledge and the level of technological advance.[243] All

[241] "Exercising the power to dispose over the genetic predispositions of a future person means that from that point on, each person, whether she has been genetically programmed or not, can regard her own genome as the consequence of a criticizable action *or omission*." Habermas J (2003) *The future of human nature* (Postscript) (Cambridge: Polity) p.82 (emphasis in original). Some omissions may be unconscious and therefore not morally culpable, although the context is important here: moral culpability may arise in relation to an unconscious omission if the omission is one that the agent should have been conscious of making (e.g. because any reasonable person ought to have been aware of the options available to them and the importance of taking responsibility for the choice).

[242] The fact that they are eventually futile might, paradoxically, be thought to make them less problematic, although this raises other issues, including about the permissibility of unnecessary interventions.

[243] See Chapter 1 above. And it is Habermas who most clearly spells out the responsibility to which we are condemned by what he would no doubt see as moral error and that Sandel explicitly describes as 'hubris': "Exercising the power to dispose over

decision making is beset by the problem that we cannot predict with certainty what is going to happen in the future. This is a problem for all moral theory because even if consequences are irrelevant to the assessment of a choice, it is still the case that the will with which one acts is future-orientated. Unlike many other decisions, though, the decision to intervene in the genome of a future person is one that involves particular kinds of consequence that are morally significant and entail distinct kinds of uncertainty.

3.40 One kind of consequence is for the well-being of the future person that could be affected in distinct ways by the procedure used. It is important to recall that we are discussing a currently unproven treatment the risks of which have not been definitively assessed. In medical decision making, decisions are often approached by 'trading off' the risks associated with different courses of action according to how different outcomes are viewed by the patient. In the cases we are discussing, clinical risks can only be a part of the story, however, as such risks come about only within the context of a voluntary reproductive project. There is an option with, in effect, no clinical risk at all, against which all clinical risks must be weighed, namely that of not having a child at all (or not having a genetically related child). Additionally, in the case of reproductive projects, the interests of the future person should be taken into account, alongside those of the prospective parents.[244] They must be taken into account, however, without knowing how the future person would value possible outcomes and in the awareness that the outcomes may themselves affect how they are valued. This is because, to a certain extent, a person's genome, as it relates to the form and experience of their unique embodiment, can be constitutive for aspects of their psychosocial identity.[245]

3.41 The wider environment within which someone is embodied generates another important asymmetry in addition to the asymmetry of agency (between those whose interests are at stake) and the asymmetry between knowledge of the present and the future. This is the normative asymmetry between the exclusion of capacity-limiting characteristics and the inclusion of alternative preferences, by which some aims may be judged as involving converging with (or conforming to) the norm whereas others may imply divergence from it (or going beyond it in some way).[246] Acknowledging the significance of this context also points to an asymmetry between act and omission, particularly where access to treatment is highly restricted and there is some risk associated with the procedure, and where others' interests and bodily rights are involved.[247] In the light of the discussion above, we can formulate a moral principle that should guide any reproductive project that involves genomic intervention. Because of the asymmetries of agency and responsibility

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the genetic predispositions of a future person means that from that point on, each person, whether she has been genetically programmed or not, can regard her own genome as the consequence of a criticizable action *or omission*." Habermas J (2003) *The future of human nature* (Postscript) p.82 (emphasis in original).

[244] For a long time (1991–2010), the Human Fertilisation and Embryology Authority (HFEA) *Code of practice* was explicitly framed by a number of moral considerations, among which was "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." For superseded editions of the *Code of practice*, see: http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/2999.html.

[245] Raising the question of psychosocial identity draws attention to the practical indissociability of different bundles of characteristics as opposed to their conceptual separablility (as when one considers actual person X but without condition P, which, in reality, they have). This consideration may serve as admonition to a way of thinking that takes disease and disability traits automatically to be of greater relative significance than other traits: they may be salient features from the point of view of identification of a person, but the value to that person as integral to their psychosocial identity may be greater than the value of having or not having any given trait.

[246] Onora O'Neill has an argument that prospective parents are not exercising procreative autonomy unless they have the intention to rear the resulting child in a way that gives it a life that is at least normal for its society. Unless they have such intentions, the state is justified in intervening in their reproductive activities; see: O'Neill O (1979) Begetting, bearing, and rearing, in *Having children: philosophical and legal reflections on parenthood*, O'Neill O and Ruddick W (Editors) (New York: Oxford University Press).

[247] For example, a prospective mother cannot be required (coerced) to have a treatment, although they might they be denied assisted reproductive technology on welfare of the child grounds if their choice was not to exclude embryos affected by a denominated serious disease.

(falling on the prospective parents rather than their offspring), epistemological uncertainty (between present states and future consequences) and normative evaluation (and its dependency on context of embodiment), this has a precautionary form.

Principle 1: The 'welfare of the future person'

Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.

3.42 While we believe that conforming to this principle is *necessary* for heritable genome editing interventions to be morally permissible, it is not *sufficient* to make them morally permissible. We will consider what other conditions should also be met below. First, however, we will give some more clarity to this welfare principle.

The implications of the welfare of the future person principle

3.43 It follows from our previous arguments that the significance of the welfare principle – specifically, what is meant by 'welfare' – is to an extent dependent on the anticipated social and technological context. Nevertheless, it is possible to say some things about this in outline.

3.44 In the first place, one of the key issues is the safety of the techniques used, specifically iatrogenic risk (the risk of adverse effects arising from the use of the technique). Safety is often described as an ethical issue in itself, although people may differ in the way they value risk. An important question to consider would be the context of this decision and what the appropriate comparator is. In Chapter 1, we have argued that the proper context in which to set this question is that of the prospective parents' reproductive project.[248] If the future person's interests were regarded as paramount, the existence of any risk could rule out any intervention[249]; at the beginning of this chapter, however, we observed how

[248] Many authors (e.g. Harris J (2016) Germline modification and the burden of human existence *Cambridge Quarterly of Healthcare Ethics* **25(1)**: 6–18; the fourth HFEA expert review panel on mitochondrial donation, available at: http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/docs/Fourth_scientific_review_mitochondria_2016.pdf) make the assumption that prospective parents' desires are inflexible and do not involve strategic, game-theoretical calculations, or that their moral claim to treatment is effectively paramount. This has the effect of making the alternatives binary (either the new technique or the unassisted reproduction) and licensing the use of risk reduction as a criterion. It is possible that Harris's claim that "many women will continue to desire their own genetically related children and will continue to have them if denied or unable to access [mitochondrial replacement techniques]" because there "is no current alternative" is another canard of the literature and deserves further examination. (Mitochondrial disease will often become evident because women have an initial affected child, although this may not be apparent until they have had subsequent children if the condition does not manifest in infancy and because of difficulty of diagnosis in childhood; see Koenig MK (2008) Presentation and diagnosis of mitochondrial disorders in children *Pediatric Neurology* **38(5)**: 305–13).

[249] If no treatment were available, a consequence would be a frustration of the prospective parents' interests; if a treatment with a non-negligible, positive risk were undertaken, the 'best' outcome would be a child as intended, but the range of outcomes also include children whose embodied being is conditioned by negative iatrogenic effects of the treatment, albeit that they would likely still enjoy 'lives worth living'. (This might be a reason for a third party to decline to assist, but not actively to interfere with the reproductive project.) For the prospective parents, however, this might not be less preferable than the range of possible outcomes available if they were to conceive without assistance. Whether they would go ahead and do this is, however, something the person providing treatment (or, at a policy level, the state authorising it) could not know. The choices change depending on the range of options available (i.e. the technological context); furthermore, the actors cannot know how the other actors value (or will value) the different outcomes, or even how they themselves will value the different outcomes, since becoming the parent of a child, with or without a given condition, has potentially transformative consequences, as is well attested (on this point, see: Paul LA (2014) *Transformative experience* (Oxford: Oxford University

significant moral weight is attached to the prospective parents' procreative interests as well, and that the interests of parents and their offspring are importantly entwined. The nature of the prospective parents' responsibilities is therefore complex.

3.45 The existence of 'alternative' approaches may be an important consideration from a risk-based perspective. Such consideration may offer an objection to innovation if there are equivalent treatments available or if the introduction of the new treatment is disproportionate to the ends to be achieved. However, who is entitled to deem that different treatments are to be regarded as 'alternatives' is an important question. (PGT may be seen as equivalent in some cases where gamete donation is not, for example.[250]) In matters of reproduction, it is axiomatic that respect for the prospective parents' autonomy requires that they are entitled to make a free choice about how they pursue their reproductive project; having the choice may only be practically significant, however, if they have acceptable options available to them among which to choose. The argument that there are alternative approaches available will also be more relevant to the innovation of new technology, where the uncertainties are greater, than to selection from among proven technologies already in use (although technologies in use will have different risk profiles that may be measured against the weight given to different reproductive preferences).

3.46 Nevertheless, we must think beyond the initial period of innovation and, making the assumption that the treatment is shown to be reasonably safe, we must consider whether having been selected/modified to fulfil certain desires or preferences is consistent with the welfare of the future person. As we have framed it, the concept of welfare ('doing well') is a broader concept than well-being ('being well'; i.e. 'healthy'). In this sense, psychosocial welfare, and not just good health, is an important consideration, although there is scope for debate as to whether good health is a necessary component of welfare. Furthermore, welfare is highly dependent on the social context.[251] We can say that, other things being equal, the avoidance of disease is consistent with the welfare of the future person. We can also say that there is no *a priori* reason that preferences beyond the avoidance of disease should not also be consistent with the welfare of the future person. Here, however, contextual factors are likely to figure more strongly.

Conclusions in relation to the interests of individuals

3.47 In relation to the interests of the individuals directly involved, principally the prospective parents and their offspring, there are plausible circumstances in which heritable genome editing interventions could be morally acceptable, subject to appropriate protections of the welfare of the future person. Perhaps the most obvious of these circumstances, because they directly affect the welfare of the future person, are that risks of adverse outcomes for offspring and subsequent generations should have been assessed through relevant research. However, it is difficult, if not impossible, to be confident that all adverse outcomes have been identified or to assess their likelihood of occurrence with confidence

Press). So a game-theoretical approach to innovation involves many different possible risks and trade-offs, despite these continually having to be reset by technological developments and life experiences.

[250] After all, for most cases of PGT, gamete or embryo donation would be a safer 'alternative' (assuming availability of donated gametes), although not, of course, an alternative that gives parents a child who is genetically related to both of them. The existence of PGT therefore suggests that there are complex reasons for differentiating different treatments.

[251] The child's alleged 'need for a father' was for a long time a statutory consideration, albeit one open to very uneven interpretation. More relevant is the family situation if a child is born into a family where one or both parents are affected by a serious disease (as is likely in cases in which genome editing offers the only prospect of an unaffected child). "Safety of a technology can certainly not be the only issue at stake – the most important, if not constitutive element of parenthood that one is able – or, more radically, alive – to care for a child." Hille Haker, Chair of Catholic Moral Theology, Loyola University Chicago, USA, in response to our refreshed *Call for evidence*.

before any actual clinical use (and before data are available from a great many clinical uses). Uncertainties of this kind beset all biomedical innovations, but they have distinctive implications in reproductive procedures where they involve not only a voluntary trial participant, but also (principally) a future person for whom adverse outcomes may be difficult, if not impossible, to redress.[252]

3.48 Two kinds of research can help to identify, although not resolve, uncertainties connected with innovation in relation to the welfare of the future person. Such research should be undertaken and supported in the public interest. The first is research into the safety and efficacy of genome editing techniques to support the development of evidence-based standards for clinical use. Since, however, the concept of welfare extends beyond purely medical description, equally important will be social research that would help to understand the welfare implications for people born following genome editing interventions (e.g. research involving people born following PGT).

3.49 While prior research, including in animal models, can provide relevant information, it cannot remove the uncertainty that must be confronted in the translation into human application.[253] The purpose of the preceding discussion of the way value is placed on having genetically related children in modern, technologically advanced societies has been to examine the interests that should provide the context for the confrontation with these uncertainties and to identify the nature of some of the responsibilities involved. We will return to the discussion of how uncertainties may be governed in practice in Chapter 4. Many of these uncertainties, particularly those related to clinical risk, are connected with the initial innovation rather than the subsequent diffusion of technology. There are potential adverse outcomes that, rather than reducing in significance, may actually increase in significance with the diffusion of the technology. Considerations relating to individuals are only one set of considerations that we must attend to in order to establish the moral permissibility of heritable genome editing interventions.[254] In the next section, we consider the indirect interests of others and the interests of the broader moral community.

Society

3.50 In the previous section we considered the interests of those directly involved in reproductive projects: the prospective parents and their future children. We concluded that the desire of people to become biological parents and, in doing so, to secure, so far as possible, the welfare of their children by using genome editing to influence their inherited characteristics gave rise to a morally powerful claim. Reproduction, particularly where it involves biomedical technologies, nevertheless takes place in a broader social and technological context. The reproduction of members of society is, at a general level, the reproduction of society – the production of the next generation. In this section, we look at the broader social considerations relating to attempts to influence the inherited characteristics of future people, including the interests of those who, while not directly involved, might be indirectly affected in morally relevant ways. This includes the way in

[252] It is expected that pregnancies following genome editing would be monitored closely, including for unexpected genomic and structural features, although the effects of the procedure may not come to light until after birth.

[253] This is perhaps analogous to the first uses of IVF or of preimplantation genetic diagnosis.

[254] We should acknowledge at this point that we received some criticism of our online public questionnaire for focusing on these issues, and it is correct that it is the interests of individuals that we were primarily interested in exploring through this methodology, although this was far from the only initiative we undertook. But the questions we posed were not just about what people thought of their own interests, but what they thought would constitute a reason for limiting the interests of others – it is more that those responding were individuals, not that we were seeking to foster an individualistic response. We were looking for individual responses, not individualistic ones.

which the pursuit of individual interests shapes the context in which others also pursue their own interests.

Shifting social norms and 'progress'

3.51 The most obvious way in which attempts to influence the inherited characteristics of future generations that may impact on society is by preferential selection of characteristics so that the composition of society (i.e. the characteristics of the individuals who comprise that society) changes over time. Research using Dutch military records going back to the eighteenth century, for example, has found that the average height of a Dutch male has increased by 20 cm in the last 200 years, a period that has seen the average Dutchman go from being among the shortest in Europe to the tallest in the world. The authors of the study attribute this growth in height (which is a strongly heritable characteristic) substantially to the relative reproductive success of taller Dutch men, as well as to nutrition and other environmental and social factors.[255]

3.52 The changing height of the average Dutchman is an example of how reproductive behaviours (reinforced by other factors) might have contributed to changing the composition of Dutch society without deliberate coordination. For this to happen it is not necessary for the choices of individuals to be noticeably constrained. In fact, the Netherlands is a technologically advanced liberal democracy with among the lowest measured levels of social inequality.[256] Reproductive technologies offer a more certain way to select the characteristics of the next generation than choice of reproductive partners. One study of Down's syndrome screening in England and Wales, for example, concluded that although the frequency of births of people with Down's syndrome had changed little over the study period, the availability of prenatal screening and termination has nevertheless had a significant impact on the number of children who would otherwise have been born with the conditions for which screening is available.[257] Heritable genome editing interventions represent a prospective reproductive technology that would further increase the power and range of reproductive choice.[258]

3.53 For individuals, heritable genome editing interventions provide a way of enabling prospective parents to have genetically related children while excluding or including certain heritable characteristics (such as predisposition to disease). At the level of populations, however, the presence or absence of people in that population with certain health-related characteristics affects the overall population health. Public health measures, such as vaccination and water fluoridation, are intended to improve the health of existing members of a population.[259] Another way to alter the characteristics of

[255] Stulp G, Barrett L, Tropf FC, and Mills M (2015) Does natural selection favour taller stature among the tallest people on earth? *Proceedings of the Royal Society B* **282(1806)**: 20150211. The study found relatively greater reproductive success for taller men with average-height women. (Taller women also experienced higher child survival, although child mortality rates were generally low in any case). They also note that "The Dutch superiority in height has been attributed to various environmental factors, including nutrition, particularly the heavy consumption of dairy products."

[256] For example, both have a very low Gini coefficient, which measures income inequality.

[257] Morris J and Alberman E (2009) Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2998: Analysis of data from the National Down Syndrome Cytogenetic Register *British Medical Journal* 339:b3794, available at: https://www.bmj.com/content/bmj/339/bmj.b3794.full.pdf

[258] While we are considering prospective genome editing technologies, we should acknowledge that a whole variety of other technologies, including industrial, automotive, financial and other technologies, may already be responsible for widespread, potentially heritable epigenetic alterations through their social and environmental effects. There is, in fact, an emerging literature on the 'epigenetic responsibility' of parents and governments for the epigenetic effects on children and citizens. See: Dupras C and Ravitsky V (2016) The ambiguous nature of epigenetic responsibility *Journal of Medical Ethics* **42**: 534–41.

[259] See: Nuffield Council on Bioethics (2007) *Public health: ethical issues*, available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Public-health-ethical-issues.pdf.

populations, however, is by influencing what sorts of people become members of the population in the first place.

Diversity

3.54 There is some scope for argument about whether, if the same reproductive options were available for all prospective parents, it would result in an increase or decrease in population diversity. One case in which a similar kind of question has arisen is that of sex selection.[260] Skewed sex ratios owing to selective abortion practices have been observed in some countries, giving rise to associated social problems. Whereas some sex diversity is currently needed for the survival of a human population, this is not necessarily the case with other characteristics.

3.55 An imaginary case in which everyone had free choice to use effective technologies to select genetic characteristics of their offspring need not lead to a significant decrease in diversity *per se* (although it may very well replace one set of diversities with another). It is possible, for example, that serious inherited disorders, at least those that are not

Box 3.2: Eugenics

'Eugenics' (a term coined by Francis Galton before the advent of molecular genetics) has a controversial history through its association with compulsory sterilisation programmes, forced euthanasia, racism and genocide in states including Germany, England and the US in the nineteenth and twentieth centuries. The growing availability of assisted reproductive technologies has expanded reproductive options significantly from the late twentieth century. This has given a new focus to disputes about the use of the term and the practices to which it is applied.[261]

A distinction is often drawn between positive eugenics (acts or initiatives that aim actively to 'improve' the gene pool of a given population) and negative eugenics (those which aim to prevent or slow any 'deterioration' of the gene pool), initially through control of who was encouraged to reproduce or discouraged (or, in some cases, prevented) from doing so.

Another distinction can be drawn according to the force and coordination with which the eugenic objectives are pursued: "strong eugenics could be defined as population-level improvement by control of reproduction via state intervention, such as happened in the 1930s. Weak eugenics could be defined as promoting technologies of reproductive selection via non-coercive individual choices."[262] Changes in the prevalence of characteristics at the population level that may result from the aggregate of individual reproductive choices have been defended as 'liberal eugenics' by a number of

[260] Sex selection can be achieved by a variety of procedures, including sex determination of embryos using PGT and selective transfer of embryos of a preferred sex. This is currently prohibited in the UK unless it is undertaken for the avoidance of a serious sex-linked disease (HFE Act 1990, ss.3–4 and Sched.2, paras 1ZA–1ZB).

[261] Philosophers Stephen Wilkinson and Eve Garrard suggest that eugenics itself can be characterised quite neutrally – a move that leaves open what kinds of actions and events should be seen as eugenic and which are acceptable and unacceptable. People can agree on a definition, even if they disagree considerably about what counts as eugenics. See: Wilkinson S and Garrard E (2013) Eugenics and the ethics of selective termination, available at: https://www.keele.ac.uk/media/keeleuniversity/ri/risocsci/eugenics2013/Eugenics%20and%20the%20ethics%20of%20selective%20reproduction%20Low%20Res.pdf.

[262] Shakespeare T (1998) Choices and rights: eugenics, genetics and disability equality *Disability & Society* **13(5)**: 665–81. The first eugenics law, authorising forced sterilisation, was passed in the US state of Indiana in 1907.

bioethicists. This is contrasted with the 'authoritarian eugenics' of state public health programmes.[263]

While there are strong objections to authoritarian eugenic programmes associated with ideologically motivated efforts to minimise the incidence of certain characteristics in a population, some have questioned the assumption that it can never be defensible for the state to pursue policy goals, such as improved population health, with interventions such as prenatal screening. They argue that the fact that the goals are approached justly matters more than the outcome.[264]

coupled with some compensating benefit, would be voluntarily eliminated (so-called 'negative eugenics'). Nevertheless, the outcome of allowing prospective parents to select, within the constraints of biology, the preferred characteristics of their children (so-called 'liberal eugenics') is difficult to predict. It might result in a society that is more homogeneous or one that is more diverse. Philosopher Nicholas Agar argues that society should adopt the same stance towards genetic choices as it does towards other kinds of life choice about which there is a diversity of views and disagreement over what is good or right.[265] Although Agar is a defender of reproductive freedom, he nevertheless acknowledges that, like other markets, the notional 'genetic supermarket' would require appropriate regulation.[266] For example, he recognises the existence of problematic biases that exist in society and the ways in which these might be supported or entrenched by the commercial availability of selective reproductive technologies.[267] Liberal approaches tend to emphasise autonomy while playing down the extent to which social choice is conditioned by social factors. Whether increased choice leads to increased variety or homogeneity might depend strongly on prevailing social factors.[268]

Shifting norms

3.56 Where reproductive behaviours change as a result of new opportunities or new conditions, what it is considered normal to do or to be may shift correspondingly and harden into new expectations. One reason to be concerned about these opportunities is that, while they may appear to offer new freedoms from the constraints of biological inheritance, expectations to comply with new norms may actually have the effect of decreasing those freedoms. It is a common speculation in bioethical debates that the separation between the act of sexual intercourse and the objective of human procreation will become normalised, with the result that, in the distant future, much or even most human reproduction will be managed by specialist scientists, in order to secure the prospective parents' preferred outcome. Visions like this extend the possibilities of freeing the genetic endowment of the next generation from the choice of reproductive partner first by broadening the choice of gametes (to include third-party donors) and second by enabling finer discriminations through embryo selection and finally cell and genome modification. Many writers have predicted that, whereas assisted reproduction

[263] Philosopher Nicholas Agar argues that liberalism requires that people should be free to make use of such technologies to pursue goods for themselves and their children in the way that they want, rather than encouraged or forced to do so by the state. Agar N (2008) *Liberal eugenics: in defence of human enhancement* (Oxford: Blackwell).
[264] See, for example: Wikler D (1999) Can we learn from eugenics? *Journal of Medical Ethics* **25(2)**: 183–94.
[265] Agar N (2008) *Liberal eugenics: in defence of human enhancement* (Oxford: Blackwell).
[266] The term 'genetic supermarket' comes from Nozick R (1974) *Anarchy, state, and utopia* (New York: Basic Books). This memorable formulation occurs in a footnote that is intended to illustrate the virtues of 'filtering' mechanisms (in this case individual preferences) over intentional design (some authority striving for an optimised human type or population).
[267] Agar N (2008) *Liberal eugenics: in defence of human enhancement* (Oxford: Blackwell).
[268] There is evidence from a previous Nuffield Council inquiry of strong social pressures to meet increasingly rigid standards of appearance; see: Nuffield Council on Bioethics (2017) *Cosmetic procedures: ethical issues*, available at: http://nuffieldbioethics.org/wp-content/uploads/Cosmetic-procedures-full-report.pdf.

has become normalised in many contemporary societies (where it was initially seen as monstrous, at least in the contemporary media), unassisted sexual reproduction may come to be seen as abnormal.[269]

3.57 The emblematic case of shifting norms is the introduction of techniques of prenatal screening for chromosomal abnormalities (of which Down's syndrome is the most familiar). It is argued that the widespread availability of screening has changed social expectations about undergoing screening and the outcome of choices following positive screening tests.[270] To be clear, it is not the choice of parents to access screening or to terminate affected pregnancies that is usually criticised, but the fact that prospective parents may feel social pressure both to undergo testing and to terminate a pregnancy. This is despite the fact that Down's syndrome, the most prevalent survivable aneuploidy, is now compatible with a high quality of life. (Terminating a pregnancy following a prenatal diagnosis of Down's syndrome is therefore regarded by some as selection on the basis of outdated views about the characteristics of people with Down's syndrome.) Shifts in behaviour of this sort may give rise to revisionary moral conclusions: what people *typically do* becomes, implicitly, what they *should do*.[271] A similar case might be encountered by a couple who have a dominant genetic disease and are also infertile. In order to have a child, they need IVF, but they then come under pressure to use PGT to screen out affected embryos in the interests of the welfare of their future child, despite the fact that they wish all their embryos to be considered for transfer, because the disease is on the Human Fertilisation and Embryology Authority (HFEA) list of conditions approved for preimplantation testing.[272]

3.58 Related concerns about the social diffusion of technology resulting in altered norms may apply to the prospect of genome editing. There are at least two plausible ways in which genome editing might become a future norm. In the first case, genome editing might become a norm for those who are undergoing IVF. Increasingly, people may come to IVF already in possession of genetic information (e.g. through prior genome sequencing or preconception screening) that they may wish to act on (e.g. to exclude a genetic risk factor for a known disorder).[273] This, in turn, may give rise to new responsibilities: both moral responsibilities for the prospective parents and professional and legal ones for the professionals involved.[274] A second case is that in which people who would not otherwise have done so may choose to undergo IVF or other forms of assisted conception in order to enable genome editing of their embryos. In the case of a prior diagnosed condition, this is the most likely route into genome editing. But the diffusion of personal genome

[269] For a recent vision of the future of human reproduction, where multitudes of embryos are routinely created in order to be screened prior to transfer, see: Greely H (2016) *The end of sex* (Cambridge, MA: Harvard University Press). This has been a device in imaginative literature and dystopian science fiction at least since the time of Ovid (2004) *Metamorphoses* (New York: W.W. Norton & Co.); see, especially, Huxley A (1932) *Brave new world* (London: Vintage), in which ectogenesis occurs via the Bokanovsky cloning procedure.

[270] See discussion in Nuffield Council on Bioethics (2017) *Non-invasive prenatal testing: ethical issues,* available at: http://nuffieldbioethics.org/wp-content/uploads/NIPT-ethical-issues-full-report.pdf.

[271] See: Lindström B, Jangard S, Selbing I, *et al.* (2018) The role of a 'common is moral' heuristic in the stability and change of moral norms *Journal of Experimental Psychology: General* **147**: 228.

[272] This example was suggested by Consultant in Clinical Genetics, Dr Susan Price, who reviewed this report.

[273] Henneman L, Borry P, Chokoshvili D, *et al*. (2016) Responsible implementation of expanded carrier screening *European Journal of Human Genetics* **24**: e1–e12; see also: Harper J, Aittomäki K, Borry P, *et al.* (2018) Recent developments in genetics and medically assisted reproduction: from research to clinical applications *European Journal of Human Genetics* **26**: 12–33.

[274] At present, for example, clinicians practising in the UK may not transfer embryos that are *known* to be affected by serious genetic condition (although embryos that have not been tested may, of course, be transferred, notwithstanding that they may be affected by an undiagnosed condition). See HFEA licence condition T86: "Embryos that are known to have a gene, chromosome or mitochondrion abnormality involving a significant risk that a person with the abnormality will have or develop: (a.) a serious physical or mental disability (b.) a serious illness, or (c.) any other serious medical condition, must not be preferred to those that are not known to have such an abnormality."

testing may reveal the possibility of novel genomic combinations that prospective parents may be keen to include or exclude.

3.59 The difficulty for those who wish to maintain a liberal stance but are concerned about the impact of genetic technologies on human diversity is that, if genome editing were widely available and accessible, they would have to allow that everyone may choose to use it; to maintain the current range of genetic diversity could, in effect, mean denying genome editing to some people who would otherwise want it, thereby compelling them to have offspring with certain 'preserved' characteristics. This would seem profoundly objectionable from the point of view of justice, and likely would have a negative impact on the psychosocial identity formation of people with those characteristics.

The expressivist objection

3.60 Even if heritable genome editing interventions were not widely taken up, leading to a detectable change in the overall composition of society, it could nevertheless be argued that simply making the technique available is objectionable. The 'expressivist objection' holds that such interventions express (hitherto implicit) negative social attitudes towards people with certain forms of embodiment and may even compound such attitudes, or exacerbate a social environment that is hostile to people with disabilities more generally. The argument was originally made in relation to prenatal screening, but would have similar force in relation to genome editing.

3.61 The expressivist objection has some traction where the consequences of the introduction of technology include negative effects on existing people with disability, and particularly where the disablement is mild and, to some extent, socially constructed. This is not the case, however, with the inherited genetic disorders that are the most likely targets for genome editing, which manifest in ways that significantly affect quality and length of life. It does, nevertheless, highlight the need to take into account the interests of those who are placed in positions of increased vulnerability as a result of the introduction of new technologies. A human rights-based approach is helpful in drawing attention to these considerations, but its utility is limited if it is only deployed defending against the negative consequences of particular proposed innovations. Complementary to this, there is a need for reflection and action on broader questions that give consideration to the sort of society to which innovation decisions collectively give rise. We discuss this kind of broader reflection below, and in Chapter 4 we propose how it might be better supported.

Social virtues of compassion, care and solidarity

3.62 Few might lament the elimination of many inherited genetic disease characteristics.[275] Nevertheless, some argue that there is a value in human fragility that would be lost in the event that disabilities were made to disappear. One way to understand this idea is that the experience of fragility can give rise to other things of value, such as care, compassion and generosity. Drawing analogies with other cases in which care is valued, bioethics scholar Erik Parens observes that many would object to the idea that we should use genetic technology to end, for instance, adolescence or old age and their associated challenges. He argues that we should treat the fragility associated with some genetic characteristics in the same way.[276] Interdisciplinary scholar Rosemarie Garland-Thomson defends a stronger view that disability is normatively valuable and should be

[275] Compare to the unlamented eradication of smallpox.
[276] Parens E (1995) The goodness of fragility: on the prospect of genetic technologies aimed at the enhancement of human capacities *Kennedy Institute of Ethics Journal* **5(2)**: 141–53.

conserved as a "potentially generative resource rather than unequivocally restrictive liability."[277] A difficulty with both Parens' and Garland-Thomson's views, however, is that they rely on members of society valuing the good of fragility enough to be willing for their children to take their turn (or their chance) as its bearers. Moral philosopher Mike Parker considers instead the place of fragility in the life of an individual, rather than of individuals in society or the human race as a whole, and argues that human flourishing comprises aspects of both strength and weakness. To attempt to eradicate negative elements of human experience in this sense would be counterproductive. As Parker says, "the concept of the best possible life is not necessarily and indeed could not be one in which all goes well."[278]

3.63 It might be suggested that there are nevertheless certain particular characteristics that exist now that should be preserved. The difficulty with this is that it turns humans into 'heritage breed livestock'. It seems difficult to make a strong case that any particular genetic characteristic should be maintained at least unless that characteristic were in some way one that was essential to what it is to be human (though this seems unlikely).[279] A much stronger case could be made for the value of diversity in the species

Box 3.3: The 'expressivist objection'

The expressivist objection to prenatal screening was first made by disability rights activists and has been defended and developed over a number of years by Adrienne Asch and a number of other disability scholars, feminists and bioethicists.[280] The argument claims that prenatal screening and other reproductive technologies used to select against the birth of disabled babies express a hostile and discriminatory attitude towards disabled people and send a harmful message about disabled people to them and to wider society.

This point has been made in different ways. Some argue that selective reproductive technologies communicate something about the lesser status or value ascribed to disabled people by society, which can not only cause psychological damage, but can also give rise to wider harms through the effects on broader social attitudes towards disabled people.[281] The message of selective reproductive technologies, it is claimed, reinforces inaccurate prejudices about the experience of disability and propagates the view that disabled peoples' lives are not worth living.[282] Another, more plausible, version of the expressivist objection says that harmful messages to disabled people are expressed not by individual users of reproductive technology, but instead by health policies that allow, fund or recommend its use to select against the birth of disabled babies.[283]

[277] Garland-Thomson R (2012) The case for conserving disability *Journal of Bioethical Inquiry* **9(3)**: 339–55.
[278] Parker M (2007) The best possible child *Journal of Medical Ethics* **33(5)**: 279–83.
[279] See the third division of the present chapter below.
[280] Wendell S (2013) *The rejected body: feminist philosophical reflections on disability* (New York: Routledge); Nelson JL (2000) The meaning of the act: reflections on the expressive force of reproductive decision making and policies *Kennedy Institute of Ethics Journal* **8(2):** 165–82; Asch A (1999) Prenatal diagnosis and selective abortion: a challenge to practice and policy *American Journal of Public Health* **89**: 1649–57*;* Parens E and Asch A (2000) *Prenatal testing and disability rights* (Washington, DC: Georgetown University Press).
[281] Hofmann B (2017) 'You are inferior!' Revisiting the expressivist argument *Bioethics* **31**: 505–14.
[282] Saxton M (2000) Why members of the disability community oppose prenatal diagnosis and selective abortion, in *Prenatal testing and disability rights*, Asch A and Parens E (Editors) (Washington, DC: Georgetown University Press); Wendell S (2013) *The rejected body: feminist philosophical reflections on disability* (New York: Routledge).
[283] Hofmann B (2017) 'You are inferior!' Revisiting the expressivist argument *Bioethics* **31**: 505–14; Holm S (2008) The expressivist objection to prenatal diagnosis: can it be laid to rest? *Journal of Medical Ethics* **34**: 24–5; Press N (2000) Assessing the expressive character of prenatal testing: the choices made or the choices made available? in *Prenatal testing*

While the expressivist objection has been prominent in debate about disability and prenatal screening, selective termination and PGT over the last two decades, a variety of criticisms have been levelled against it. A common objection is that any negative message that might be communicated by these uses of reproductive technology need not be about disabled individuals themselves; it is possible to disvalue a condition that gives rise to disability at the same time as valuing people who have the condition as highly as those who do not.[284] Another response is that if a harmful message sent by the use of reproductive technology is sufficient justification for not using it, this might entail also that we should not attempt to treat or cure disability at all, and that it would not be wrong to bring about disability deliberately, conclusions that most people would find unacceptable.[285] It has also been argued that the motivations and beliefs that underlie *individual* decisions about reproductive technology are so diverse that no single message is clearly communicated.

Whether or not it is warranted to regard selective reproductive technologies as necessarily conveying any message, their availability might nevertheless distress or offend some disabled people. Empirical work in this area has found that some disabled people do find the availability of reproductive technology to select against disabled babies distressing, devaluing or offensive.[286]

in general as insurance against changing conditions, although this could not justly be used to require a particular person to have (or, which may amount to the same thing, to refuse them the means to avoid having) that characteristic. Restrictive measures are in any case unlikely to be necessary to preserve fragility either at the social level (Parens) or at the individual level (Parker). Sociologist Tom Shakespeare dismisses predictions of an end to disability by observing that instances of disability will always arise (e.g. spontaneous mutations, post-natal illness, accidents, ageing) and applications of genome editing targeting inherited genetic disability will not have a significant impact on societal diversity or what is considered to be normal.[287] Though what constitutes fragility and disability may change in relation to evolving norms and changing conditions, they will always be with us.

3.64 Although human diversity itself may not be under significant threat from genome editing interventions, changes in the composition of society may have a transitional impact on individuals.[288] If there are fewer people with a given range of disabilities, the general level of familiarity with and social acceptance of those conditions may decrease. At the same time, specialist medical expertise or skills are likely to become rarer, and there may be less investment in research or measures to alleviate any specific adverse physical effects

and disability rights, Asch A and Parens E (Editors) (Washington, DC: Georgetown University Press)*;* Shakespeare T (1998) Choices and rights: eugenics, genetics and disability equality *Disability and Society* **13(5)**: 665–81.

[284] Malek J (2010) Deciding against disability: does the use of reproductive genetic technologies express disvalue for people with disabilities? *Journal of Medical Ethics* **36**: 217–21. Shakespeare T (2006) *Disability rights and wrongs* (London: Routledge).

[285] McMahan J (2006) Is prenatal genetic screening unjustly discriminatory? *Virtual Mentor* **8(1)**: 50–2. McMahan J (2005) Causing disabled people to exist and causing people to be disabled *Ethics* **116(1)**: 77–99; Harris J (2001) One principle and three fallacies of disability studies *Journal of Medical Ethics* **27**: 383–7; Buchanan A, Brock D, Daniels N, *et al.* (2000) *From chance to choice: genetics and justice* (Cambridge: Cambridge University Press).

[286] Boardman FK (2014) The expressivist objection to prenatal testing: the experiences of families living with genetic disease *Social Science & Medicine* **107**: 18–25; Barter B, Hastings RP, Williams R, *et al*. (2017). Perceptions and discourses relating to genetic testing: interviews with people with Down syndrome *Journal of Applied Research in Intellectual Disabilities* **30(2)**: 395–406.

[287] Research interview with Tom Shakespeare, Professor of Disability Research, University of East Anglia.

[288] We might notionally separate issues to do with the transition to a future state of affairs (in which some might be transiently disadvantaged) and issues to do with living in that future state (to do with the moral acceptability of that state or its desirability compared to alternative possibilities). The choice of technology is, by definition, not a 'zero-sum game', although the notion of what direction constitutes 'progress' is highly problematic.

of disability or into ameliorative environmental adjustments.[289] This is at least a reason to pause and reflect on whether the promotion of genome editing is the only or the most appropriate response to the existence of certain forms of disability, one that embodies a kind of 'technological solutionism' that attempts to address with a technological solution what is, at least partly, a social challenge.[290]

Equity and justice

3.65 The structure of norms presupposes a distinction between what is within or in conformity with the norm and what is beyond or in tension with it. Even when norms shift, the idea that this distinction can be made remains constant. It is possible, however, that people or their morally considerable interests will find themselves in a different relationship to the norm as the use of new technologies diffuses. As we argued in Chapter 2, although shifting social norms are not necessarily a bad thing in themselves, they can affect the distribution of advantages and disadvantages among people.[291] In other words, there may be winners and losers: those who benefit and those who will find their interests harder to pursue or secure, and there may be more or fewer people in each category. Even if all benefit, there may be concerns if some benefit substantially more than others.

3.66 Justice concerns are likely to arise where access to benefits is unequally distributed, where the potential benefits and risks are distributed differently (so that some enjoy a greater proportion of the benefit while others bear more of the risk) and where this distribution is linked to the distribution of other goods (so that the effect is to compound existing inequalities or entrench advantages).[292] This would be the case if, for example, the service were only available at a cost that would be prohibitive to some who might wish to use it. This is, of course, the case for many consumer goods, especially luxury goods. But certain goods are more fundamental to leading a fulfilling life, and for this reason are often the sort on which the protections of human rights have traction.[293] Goods such as basic healthcare and education generally fall into this category. Though significantly different and more complex than basic healthcare, we have suggested above that the opportunity to have genetically related offspring is a good that is widely regarded in this way.[294]

3.67 In order to consider whether a shift of norms may have an undesirable outcome, it is necessary to refocus consideration from the desirability of individual choices to the kind of society that those choices might bring about. In other words, it is necessary to imagine

[289] On the other hand, it is not an argument in favour of encouraging the birth of people with disabilities such that their greater prevalence would encourage these things – the fact that such measures are taken reveals something about the asymmetry between having the condition and other forms of embodiment.

[290] 'Technological solutionism' – the idea that the 'friction' and difficulties humans experience can be removed by technology – is critiqued (although not principally in relation to biotechnology) by controversialist and technology commentator Evgeny Morozov in Morozov E (2014) *To save everything, click here: technology, solutionism and the urge to fix problems that don't exist* (New York: Penguin Books).

[291] The question of moral boundaries will be addressed in the third division of the present chapter. On the relationship between social norms and reported moral attitudes, see: Lindström B, Jangard S, Selbing I, and Olsson A (2018) The role of a 'common is moral' heuristic in the stability and change of moral norms *Journal of Experimental Psychology: General* **147(2)**: 228–42 (quoted above).

[292] On the incongruent distribution of potential benefits and risks, see: Beck U (1992) *Risk society: towards a new modernity* (London: Sage Publications).

[293] These goods might be ones connected with Aristotelian views about 'human flourishing' (see, for example: Kleinig J and Evans NG (2013) Human flourishing, human dignity, and human rights *Law and Philosophy* **32**: 539–64), though this conclusion may equally be reached by a social contract theory (see, for example: Rawls J (1971) *A theory of justice* (Cambridge, MA: Harvard University Press)) or by other theoretical paths.

[294] Part of the complexity arises from the fact that, unlike healthcare, one of the consequences may be to generate additional people with their own moral claims.

the future of the society that shapes itself partly in response to the particular technological forms in play.[295] The purpose of this is not the vain attempt to predict the future; it is rather an attempt to explore moral responses to different envisioned future states of affairs (and particularly to explore differences among people in how they evaluate those states of affairs). Doing so can help to illuminate concerns about distributional effects and the potential for unintended consequences. It can also help to avoid 'sleepwalking' into a future that is less than desirable either because interventions that could have been beneficial are prohibited because of imagined harms or, conversely, because harmful outcomes occur that could have been avoided through foresight and precautionary measures. We suggested a possible starting point for these deliberations in Chapter 2 when we considered how the use of genome editing might grow beyond the rare cases of first use, migrating to other indications as conditions permitted. In the present chapter, we have started to think about the social implications of possible technological innovations and of decisions to apply them in individual cases. The further step is to imagine what it might be like to live in such a world as differently embodied inhabitants and how different socio-technical conditions would affect the fulfilment or frustration of interests.

3.68 It is beyond the scope of this report to reflect the range of futures that contain the various possible genomic technologies (or none), and to do so in a report such as this would be inadequate in any case. What we propose is more modest; namely, to examine and juxtapose the different ways of valuing that those who have different interests in the matter bring to it. This can be achieved by engaging with the views of those whose interests are affected by heritable genome editing interventions, expressed in their own terms and understood against the background of their own values and experiences.[296] This is not simply those who may wish to use genome editing techniques in the first instance, but also those whose interests are less directly affected, in particular any who are in (or may be placed in) positions of unequal vulnerability. Since a shift in norms can engage the interests of those who hitherto might consider themselves to be disinterested observers and to the extent that these normative developments re-pattern the moral fabric of society, this is potentially everyone.[297] We propose here a principle of social justice and solidarity to secure that if heritable genome editing technologies are introduced, their use is restricted to cases they should not result in unfair advantage for certain individuals or groups or unfairly disadvantage for others. In Chapter 4, we make recommendations to facilitate this kind of engagement and thereby to help to ensure that the social justice and solidarity principle is addressed.

[295] In other words, to explore 'socio-technical imaginaries': see Chapter 2 above; see also Harvard University (2018) The sociotechnical imaginaries project, available at: http://sts.hks.harvard.edu/research/platforms/imaginaries/.

[296] Some preliminary exploration of these issues was carried out through our public questionnaire and through the series of research interviews that formed part of the Nuffield project that includes the preparation of this report (see Appendix 1). The findings of these will be available for further discussion.

[297] Insofar as the aim of social engagement is to inform policy making, it need only focus on the illumination of interests and values rather than the objective of reaching consensus. A virtue of this sort of approach is to be able to attend to voices that may be obscured in the outcomes of decision-focused debates and particularly in aggregative procedures (e.g. polls or surveys). On this, see: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf.

Principle 2: Social justice and solidarity

The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.

Conclusions in relation to the interests of others and of society

3.69 In the first part of this chapter, we found that the desire of parents to have genetically related children was widely recognised as an interest having positive social value. We found that there is a strong moral claim to be allowed to pursue this interest without interference and that may, in some cases, enjoin positive assistance.[298] We also found that the intention to use genome editing to secure that children have genetic characteristics connected with their welfare (e.g. the absence of heritable disease) was morally approvable. However, we noted that there were limits: not all uses of genome editing to improve the welfare of future people were acceptable. We had to consider the wider implications, including the indirect effects on others and conformity with the system of moral norms that implicitly underpin the moral community.

3.70 We considered the possibility of heritable genome editing interventions changing the composition of populations and changing social norms and expectations of behaviour, as well as the implications for social diversity and for the experience of disabled people in particular. We found that if heritable genome editing interventions are to be introduced, it will be important to do so in a way that does not increase unfairness and disadvantage. We recognise the danger of consideration of the full range of relevant interests being obscured or distorted by a focus on the immediate goals of prospective parents, perhaps because others are less directly affected, perhaps only after a considerable time and perhaps, albeit in greater numbers, to a lesser extent individually. Certain consultative or democratic procedures, particularly those that are focused on a binary choice constructed around a particular solution (e.g. 'permit X' versus 'do not permit X') tend to obscure these considerations by requiring the polarisation of views. This works against the possibility of constructive engagement between more complex and nuanced positions and of discovering circumstances that can support consensus.

3.71 Recalling the discussion of technological innovation and public interest in Chapter 2, we conclude that genome editing interventions should be introduced only after there has been a sufficient opportunity for broad societal debate.[299] (We will return to what this means in practice and how it might be encouraged in Chapter 4.) It is particularly important that the voices of people who may be collaterally affected are attended to within this debate, particularly those who may be placed in positions of unequal or increased vulnerability. Particular efforts are therefore needed to engage in open and

[298] The cases in which support is enjoined will depend partly on the technological pathways available and would depend partly on the social context (whether funding is available and equitable provision is possible, etc.).

[299] 'Broad societal debate' is a formulation that is becoming common in relation to genome editing and related questions. In a dynamic, law-governed society, where a decision must be made between options with different value profiles (and 'doing nothing' has consequences like other options), we do not believe that it is necessary that the debate results in a 'broad societal consensus' as some have suggested; see, for example: Hurlbut JB, Jasanoff S, Saha K, *et al.* (2018) Building capacity for a global genome editing observatory: conceptual challenges *Trends in Biotechnology* **36(7)**: 639–41.

inclusive consultation with those whose vulnerability to adverse impacts might be increased by the introduction or extension of heritable genome editing interventions.

Humanity

Transgenerationalism

3.72 The paired base structure of DNA, which encodes the genome, enables the 'copying mechanism for the genetic material' that allows it to be transmitted from generation to generation.[300] Our discussion so far has focused on intergenerational genome modifications; that is, modifications that alter the genetic endowment passed between one generation of progenitors and the next generation, their offspring.[301] One significant difference between editing an embryo and somatic gene therapies that are being developed for the treatment of certain genetic diseases (and also for non-therapeutic purposes) is that the modifications in the embryo are, in principle, replicated in every cell nucleus in the organism and, as such, also enter the future person's 'germ line'.[302] This means that the modification may be passed on via their gametes (eggs or sperm) and is capable of being inherited by descendants, potentially down an indefinite number of future generations, until it is lost through normal mechanisms of recombination and segregation (as occurs with any other allele), or it is deliberately reversed through further intervention, perhaps involving genome editing, or simply through not having children.

3.73 This possibility of transgenerational inheritance engages questions of responsibility not only to the next generation, but also to future generations. Some would consider it a benefit to be able to spare their descendants from the likelihood of an undesired characteristic resurfacing in each new generation. Others would see this as an arrogant constraint on their freedom, an attempt to fit them for a particular kind of life that they may not want. The potential for transmission of changes through many generations compounds concerns about safety. It introduces the worry that potential adverse effects might incubate without manifesting for long periods, only becoming evident late in life or even after several generations, by which point they might have diffused to multiple descendants.[303] As well as the simple numerical expansion, any such diffusion could involve distributional inequalities as it would affect particular families.[304] On the other hand, if a highly penetrant, inherited adverse effect were identified at the first or second generation of descendants, and if we assume that genome editing technology will be at least as effective by the second generation as it was at the first (and probably much more so by later generations), it would allow subsequent generations to make a further intervention to reverse or rewrite the modification in their own offspring. Though this

[300] Crick FC and Watson JD (1953) Molecular structure of nucleic acids, a structure for deoxyribose nucleic acid *Nature* **171(4356)**: 737–8.

[301] There is some uncertainty that a specific alteration will be passed on uniformly. There are rare reversion mutations, recombination events and even interacting/compensating/complementing mutations that may affect the transmission of the specific alteration through generations of cells and people.

[302] Some 'somatic' therapies may also result in modifications to reproductive cells and could therefore be passed on to descendants.

[303] Genetic variations generally have a particular consequence only in the context of a whole genome (except in rare cases such as single gene disorders, discussed in Chapter 1, which seem to have near-100% penetrance). Except where the effect is analogous to that of a single gene disorder, it would be difficult to isolate the impact of an introduced variant as the cause of an observed harm (or, therefore, as being the automatic target for further remedial intervention).

[304] This is true, of course, of any genetic trait that is strongly determinative, like the single gene disorders discussed in Chapter 1. Haemophilia is known to have passed into a number of European royal families in the nineteenth and twentieth centuries through descendants of Queen Victoria. In many cases, the burden of disease can have a negative and compounding effect on the economic and social circumstances of affected families. (See, for example: Angelis A, Tordrup D, and Kanavos P (2015) Socio-economic burden of rare diseases: a systematic review of cost of illness evidence *Health Policy* **119**: 964–79; Genetic Alliance (2016) *The hidden costs of rare disease: A feasibility study*, available at: https://www.geneticalliance.org.uk/media/2501/hidden-costs-executive-summary_21916.pdf.

situation is quite unlikely, it may not, in any case, be worse than the situation of their antecedents, so restoring the original variant may still be undesirable. It is impossible to assign likelihood to such speculative outcomes in the abstract, but it may also be beside the point: we can try instead to identify the requirements and limits of our responsibilities to future generations. Just as we did in relation to first-generation descendants in the first part of the present chapter, we confront again the problem of finding a way for the interests of those who do not yet exist to figure in our moral reasoning about the circumstances of their existence, although now in a much more attenuated way.[305]

3.74 The notion that responsibilities or obligations are owed to future generations is not only relevant to decisions about human reproduction. It has been particularly prominent in recent decades in public and academic discourse on subjects ranging from developments in nuclear power to (especially) environmental degradation and global climate change.[306] Recently, concerns about environmental and molecular harms have come together in the identification of epigenomic effects of environmental conditions for which human activity is responsible.[307] Some scholars argue that the power that present generations wield over the conditions of life of their descendants requires us to develop a distinctive concept of 'intergenerational justice'.[308] This would entail, as a minimum, a responsibility on present generations to secure the conditions for an acceptable level of welfare for succeeding generations consistent with the environmental principle of sustainability.[309] While at first blush sustainability may seem like a conservative principle, in a dramatically changing socio-technical and environmental context, it may require the contemplation of more radical action.

3.75 It is beyond doubt that recent generations of humans in industrialised countries have in many ways made the shared environment less sustainable for their descendants.[310] These effects are so significant that many scientists have begun to characterise the period of their incidence as a new aeon in geological time: the Anthropocene.[311] Humans

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[305] See: Gosseries A and Meyer LH (2009) Introduction – intergenerational justice and its challenges, in *Intergenerational justice*, Gosseries A and Meyer LH (Editors) (Oxford: Oxford University Press); nevertheless, some scholars have attempted to give content to the rights of future generations; see: Skene L and Coady CT (2002) Genetic manipulation and our duty to posterity *Monash Bioethics Review* **21**: 12–22; Beyleveld D, Düwell M, and Spahn A (2015) Why and how should we represent future generations in policymaking? *Jurisprudence* **6**: 549–66.

[306] Explicit appeals to responsibilities to future generations are found in various international policy instruments concerned with the development and protection of the natural environment and cultural heritage, such as the 1972 UNESCO Convention for the Protection of the World Cultural and Natural Heritage (UNESCO (1972) Convention Concerning the Protection of the World Cultural and Natural Heritage, available at: http://whc.unesco.org/en/conventiontext/); the UN Framework Convention on Climate Change (UN (1992) United Nations Framework Convention on Climate Change, available at: https://unfccc.int/resource/docs/convkp/conveng.pdf); the Convention on Biological Diversity (UN (1992) Convention on Biological Diversity, available at: https://www.cbd.int/doc/legal/cbd-en.pdf); and the Rio Declaration on Environment and Development (UN (1992) Rio Declaration on Environment and Development, available at: http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm) adopted in 1992; and with human rights, such as the 1993 Vienna Declaration and Programme of Action as adopted by the World Conference on Human Rights (World Conference on Human Rights (1993) Vienna Declaration and Programme of Action, available at: http://www.ohchr.org/EN/ProfessionalInterest/Pages/Vienna.aspx)

[307] See the notion of 'epigenetic responsibility' mentioned above.

[308] Goodin RE (1985) *Protecting the vulnerable: a reanalysis of our social responsibilities* (Chicago: University of Chicago Press); see also: Caney S (2018) Justice and future generations *Annual Review of Political Science* **21**: 475–93.

[309] Previous Nuffield Council reports have invoked the notion of stewardship, which places a higher level of requirement than sustainability; see, for example: Nuffield Council on Bioethics (2011) *Biofuels: ethical issues* (London: NCOB).

[310] References to the 'natural environment' refer 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 (e.g. urban and agricultural areas). Ecosystems within the natural environment may be highly integrated (with high interdependency between elements) and dynamically stable over time.

[311] This may be dated from the mid-twentieth century, from the Industrial Revolution in the late-eighteenth century or even from the Agricultural Revolution in the Neolithic era depending on what evidence (e.g. from the atmosphere or lithosphere) is

who have adapted slowly to a particular biological niche may be found to be ill fitted to their rapidly changing conditions of existence. Climate change, for example, will undoubtedly make significant parts of the earth much less hospitable to humans.[312] Meanwhile, air pollution and other DNA-damaging toxins that people imbibe or are exposed to with relatively little choice are increasing in many densely populated parts of the world.[313]

3.76 It has been suggested that genome editing could offer a remedy to this predicament by allowing the introduction of characteristics that will fit future generations better for the conditions in which they may be required to live.[314] Because genome editing potentially enables humans to direct their own evolution and the evolution of co-inhabitants of the planet at a molecular level, this could take effect at a pace that would be unachievable by undirected evolutionary processes, but potentially demanded by the rate of environmental catastrophe. Such a project would be reckless at present, given the enormous uncertainties implied in attempting to direct evolution at the molecular level.

3.77 Where there is significant uncertainty about the consequences of the application of a technology and reason to believe some outcomes could be catastrophic, some version of the well-known (but unevenly interpreted) 'precautionary principle' is often invoked.[315] In the scenario, if genome editing were the only option, both choosing and not choosing that option have potentially catastrophic outcomes (blighted lives of future people on the one hand and the realisation of an existential threat on the other). Thankfully, genome editing is not the only solution, although none of the currently identified solutions is easy or certain.[316] Nevertheless, although there are many different interpretations of the precautionary principle, at minimum it permits taking action in the present even in the absence of clear evidence of the likelihood of a harm that might occur in the future. Accordingly, the principle would at least seem to mandate further research and

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 2008. See also: http://anthropocene.info/.

[312] This example was given in our public questionnaire. A more radical case might require humans to leave an earth become inhospitable. Such a scenario is developed by speculative fiction author and futurologist, Neal Stephenson (Stephenson N (2015) *Seven eves* (London: Harper Collins Publishers). Geneticist George Church has suggested a number of feasible genetic modifications based on well-characterised genetic variations that would fit human beings for prolonged space flight (see: MIT Technology Review (2017) *Engineering the perfect astronaut*, available at: https://www.technologyreview.com/s/604142/engineering-the-perfect-astronaut/). A reason to take this seriously is, perhaps, that US 'Big Science' agency NASA is also taking notice; for example, it has an active research theme on The Health Risks of Extraterrestrial Environments (THREE) (see: https://three.jsc.nasa.gov/#section=main).

[313] This was discussed under the rubric of the 'biotechnology wager' in Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf; see also "the problem of intergenerational buck-passing" described in Gardiner SM (2006) Protecting future generations: intergenerational buck-passing, theoretical ineptitude and a brief for a global core precautionary principle, in *Handbook of intergenerational justice*, Tremmel J (Editor) (Cheltenham: Edward Elgar Publishing). It is trenchantly stated in a passage from the Brundtland report; see: Brundtland G, Khalid M, Agnelli S, *et al.* (1987) *Report of the world commission on environment and development: our common future* (United Nations), available at: http://www.un-documents.net/our-common-future.pdf). As a matter of policy, this could be a rational response if there is a good reason to expect that future technology will come to the rescue; the difficulty with such a policy is the fundamental inductive uncertainty of technological development.

[314] This is explored in Baylis F and Robert JS (2005) Radical rupture: exploring biological sequelae of volitional inheritable genetic modification, in *The ethics of inheritable genetic modification: a dividing line?* Rasko JEJ, O'Sullivan GM, and Ankeny RA (Editors) (Cambridge: Cambridge University Press).

[315] The precautionary principle was taken up into legislation in the United Nations Conference on Environment and Development (1992) Rio Declaration, Annex I, available at: http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm, Principle 15; variations have since appeared in many other reports and legal instruments, and a large critical literature has developed around the principle and particularly around inappropriate attempts to apply it as a risk management tool in conditions of uncertainty; see: Harding R and Fisher EC (Editors) (1999) *Perspectives on the precautionary principle* (Leichhardt: Federation Press).

[316] See Runciman D (2015) A tide of horseshit *London Review of Books* **37(18)**: 34–6.

development of genome editing technologies as a way of hedging against future threats.[317]

3.78 In the first part of the chapter, in examining the ethics of genome editing in relation to individuals, we did not conclude that there was a knock-down objection to (safe, effective) heritable genome editing interventions so long as they were consistent with the welfare of the future person. At the end of the second part of the chapter, we concluded that such interventions would be wrong insofar as they produced injustice, but our conclusion was not categorical; we did not say that the interventions were wrong in principle. The arguments we discussed were focused on heritable genome editing interventions at the individual and social levels.[318] The examples above start to broach the implications of transgenerational genome editing (extending across an indefinite number of future generations) and of modification at the species level. We began this chapter with the question of why we should recognise a value attached to enabling people to have the children they want. We have suggested, for the sake of argument, that genome editing could contribute to the salvation of the human species or perhaps lead to it being superseded. The reason for doing so is to illuminate a further question: why should we attach a value to the survival of the human species at all?

Transhumanism

3.79 In this section, we will discuss the suggestion that genome editing could lead to the self-overcoming of the human species. We will consider, in particular, the significance of the relation between the 'human genome' and the nature of human being. The discussion of this question will bring us, finally, to the question of whether there is anything about genetic modifications *per se*, or certain classes of genetic modification, that mean they should be categorically prohibited because they offend against something of fundamental significance for the nature of human being itself.

Genealogy, heritage and dignity

3.80 Two senses in which intergenerational genome editing is morally troubling to a conception of humanity informed by the discoveries of contemporary genomics are, first, that it threatens the integrity of human genetic inheritance and, second, that it threatens the integrity of human genomic identity. The first concerns interference with the line of transmission of the genetic endowment between generations, which, as it were, links the notional 'human family' together; the second concerns interference with the boundary conditions of the notional class of human genetic endowments – what distinguishes the 'human family' from non-human beings. Many scholars and some existing legal instruments may be taken to imply that either or both of these forms of interference would be (or might be) regarded as morally impermissible.[319] Such objections are often stated, particularly in some human rights discourses, in terms of violations of 'human dignity'.

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[317] There is a risk of creating a damaging expectation through overpromising and reliance on technological solutions in such cases. This underlines the value of genetic variation for population resilience (see Chapter 1 above).

[318] Some authors see this as sufficient. Howarth has argued that there is a 'chain of obligation', where responsibilities to future people follows from our responsibilities to the generation that will overlap with ours; see: Howarth RB (1992) Intergenerational justice and the chain of obligation *Environmental Values* **1**: 133–40; see also: Skene L and Coady CJ (2002) Genetic manipulation and our duty to posterity *Monash Bioethics Review* **21**: 2.

[319] These correspond, rather nicely, to the outcomes that, respectively, the Oviedo Convention and the Universal Declaration on the Human Genome and Human Rights seek to prohibit. On the Oviedo Convention particularly, see Mills PFR (2017) Lame ducks might fly: genome editing, global consensus and geo-ethics *Bioethica Forum* **10(2)**: 68–70.

3.81 The first thing to notice is that, from a descriptive point of view, these cases may not be particularly troubling if the intervention is simply to replace a genetic variant in a gamete or embryo with a variant that may be found elsewhere in the family pedigree or in the wider human population.[320] A typical variant is often called a 'wild-type' variant, although, like other animal species, humans exhibit a range of normal variation, and characterising variants as 'atypical' or 'mutant' is often heavily value laden. Actual wild-type variations are, however, merely a descriptive subset of the set of possible variations (those that evolution could have brought about and – for all we know – already exist somewhere but are yet to be identified by population genome sequencing). While it is clear that some combinations of characteristics are biologically prohibited because they could not coexist in the organism (i.e. they would be lethal to it), for those combinations that remain, the fact that they occur in any living being may be largely a result of particular reproductive encounters and DNA mutagenesis. It would seem unreasonable, particularly given changing environmental conditions and evolutionary pressures, to imagine that the variations observed in existing or extinct populations represent the final range of possible, properly human genomic states.

3.82 The kind of 'genomic essentialism' that would link human dignity or human rights to the possession of a particular kind of genome seems incoherent since the human genome is not a single, stable thing, nor is it distinct in all particulars from the genomes of other organisms.[321] The first argument against directing evolution away from the 'wild type' is that it would be reckless to do so in practice. This is because of the relative poverty of current knowledge and the fact that we do know that evolution is costly (in terms of false trails), which could translate into a real human cost, and we probably do not know, at present, how to do better by rational design. Such an objection applies much less convincingly, however, to the case in which a given variation is altered to a well-characterised wild-type variation found in a near genetic relative. It is furthermore a prudential argument, not a categorical one.

3.83 The concern that animates categorical opposition to genome editing, once the worry about the safety of the technique is stripped away, seems to be less about the nature of future people than a concern about the intervention of humans, at the molecular level, in the process of their own evolution. However, if we were not willing to accept this as an objection in relation to individuals, as we were not when we discussed it in the first part of the present chapter, it seems that we have no better reason to accept it in relation to the future of the species.

Justice and human nature

3.84 There are nevertheless reasons to be concerned about access to genome editing and other biotechnologies from the point of view of social justice. In the second part of the present chapter, we considered the possibility that aggregate individual choices could lead to a change in social norms connected with a change in the composition of the human population. We noted how this happens through reproductive partner choices and potentially also by epigenetic modifications.[322] Concerns have long existed that

[320] There may be concerns if it were replaced with a variant that caused or predisposed to disease (a dysgenic intervention), but those concerns arise for other reasons, not because the resulting person lacks humanity or human dignity.

[321] HFEA Ethics and Law Committee paper ELC (05-06) 01 ('And if the body were not the soul…': the status of embryos created artificially from human and non-human components", 17 May 2006), available at: http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/2124.html.

[322] It is important to consider the extent to which prospective genome editing technologies will be merely tools that enable their users to achieve a certain range of normatively good and bad ends or the extent to which the technologies themselves could embed normative values and objectives, skewing that range of ends in a particular way. See: Winner L (1980) Do artifacts have politics? *Daedalus* **109(1)**: 121–36.

genetic technologies could lead to the emergence of a 'genetic underclass'.[323] Since the early 1990s, particularly in the US, these concerns have been focused on what genetic profiling might reveal about genetic predisposition to disease, which might make people 'unemployable and uninsurable'.[324] Genome editing would compound these concerns in a different way if it were the case that access to genome editing technologies were distributed unequally (e.g. as a result of cost or variable public service provision), potentially resulting in socially advantageous genetically conditioned characteristics becoming concentrated in certain groups and families, while other (disadvantageous) characteristics would become concentrated in other groups.[325]

3.85 In a number of generations, it is imaginable that a schism might arise between the 'gene rich' and 'gene poor', which could have the effect of undermining 'genetic solidarity' as a basis for moral treatment of others. An extrapolation of this idea imagines a distinction arising between the 'merely human' and something beyond the human – a 'post-human'– in a way that sets up a potentially agonistic opposition. It is possible to imagine this not

Box 3.4: Human dignity and human rights

The concept of human dignity has a long history and has played an important role in the fields of philosophy, politics and law.[326] There are competing views about what human dignity consists in and the role it should play in policy and legislation. Disagreement exists over whether there is any single idea at work in the different discourses in which human dignity is invoked.

In philosophical contexts, human dignity is often appealed to by theorists aiming to articulate what is special or distinctive about human beings. It is taken to be a feature possessed by humans but not other animals, one that grounds the unique value and (moral) status of human beings. As such, questions about human dignity relate in important ways to questions about personhood, autonomy, rationality, morality and other concepts associated with normative notions of humanity. Human dignity also features in accounts of other important philosophical notions: in 'capability' approaches to social justice, for example, the notion of human dignity is key in identifying the particular capabilities to which people are entitled.[327]

The notion of human dignity has also been widely invoked in legal instruments in many parts of the world, particularly following the end of the Second World War, and is foundational in human rights law. The 1948 United Nations Universal Declaration of Human Rights states, in Article 1, that "all human beings are born free and equal in

[323] See Human Genetics Commission (2002) *Inside information: balancing interests in the use of personal genetic data* (London: HMSO). The concern was taken seriously enough at the time to require the UK Government to provide reassurance in its 2003 white paper *Our inheritance, our future* (Department of Health (2003) *Genetics white paper: our inheritance, our future: realising the potential of genetics in the NHS*). It was discussed in the Council's 2010 report, 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.

[324] Lee C (1993) Creating a genetic underclass: the potential for genetic discrimination by the health insurance industry *Pace Law Review* **13**: 189; Wolf SM (1995) Beyond 'genetic discrimination': toward the broader harm of geneticism *The Journal of Law, Medicine & Ethics* **23**: 345–53.

[325] This concern rests once again on genetic exceptionalism and essentialism and the context dependency of 'desirability'; in reality, we are probably talking mostly about a relatively small number of well-characterised, inherited genetic diseases rather than more complex traits.

[326] It has been suggested that the range of discourses and disciplines in which the concept of 'human dignity' features is one of the reasons that endeavours to produce a single account or theory of the concept have been frustrated.

[327] Nussbaum M (2006) *Frontiers of justice: disability, nationality, species membership* (Cambridge, MA: Harvard University Press).

dignity and rights."[328] The notions of inviolability, inalienability and universality are important associated concepts, and the idea that human dignity both imposes hard limits on how people can be treated and is an inherent feature common to all human beings, irrespective of their nationality, race, gender or other characteristics, is key in its role in international and human rights legislation.

Nevertheless, it has been argued that there is no single, coherent concept of human dignity. It has been observed, for example, that the notion can be applied for very different purposes by legislators and that there are both 'empowerment' and 'constraint' conceptions of human dignity that can be used variously for liberal or conservative policy ends.[329] Moreover, there are problems with specifying any feature(s) common to all human beings with which human dignity might be identified; philosophical accounts of human dignity that tie the notion closely to ideas about personhood or autonomy, for example, can encounter problems in accounting for the dignity (and rights) of young children or those with severe mental impairments.[330] Accounts of dignity that instead view it as a fundamental, metaphysical property of human beings have been criticised for being obscure or unreasoned.[331] Strong associations have been made between the concept of human dignity and the human genome, most notably in the Universal Declaration on the Human Genome and Human Rights.[332]

Whereas human dignity has been advanced by some as the basis of human rights, the coherent functioning of human rights discourse does not depend on accepting this claim.[333]

being merely biologically expressed, but also biologically consolidated.[334] Such a future has been imagined by both philosophers and the makers of science fiction as a thought experiment that can shed light on the embedded values and consequences of our present actions.

3.86 In departing from human nature and its particular forms of embodiment, it is claimed that a post-human being might no longer be committed to human forms of morality. Such a being might stand in relation to the present era of human beings in much the same relation as human beings now stand to non-human animals.[335] This concern is expressed by scholars in the dignitarian tradition who see an essential relation between

[328] This is also in Article 1 of the Charter of Fundamental Rights of the European Union ("Human dignity is inviolable. It must be respected and protected").

[329] Beyleveld D and Brownsword R (2001) *Human dignity in bioethics and biolaw* (Oxford: Oxford University Press). Human dignity has been used as a justification of diametrically opposed policies; for example, both to justify a ban on human embryonic stem research (Germany) and to permit it (Israel). See, for example: Gottweis H and Prainsack B (2006) Emotion in political discourse: contrasting approaches to stem cell governance in the USA, UK, Israel and Germany *Regenerative Medicine* **1(6)**: 823–9. This does not stop it providing a helpful focus for exploring these differences in international debates.

[330] For these reasons, Leon Kass and others adopt a view of dignity as a metaphysical property possessed by all human beings (see: Kass LR (2004) *Life, liberty and the defense of dignity: the challenge for bioethics* (New York: Encounter Books). The Beyleveld and Brownsword account aims to circumvent this challenge by adopting an extended conception of autonomy that is able to capture borderline cases (Beyleveld D and Brownsword R (2001) *Human dignity in bioethics and biolaw* (Oxford: Oxford University Press)).

[331] Ashcroft RE (2005) Making sense of dignity *Journal of Medical Ethics* **31**: 679–82.

[332] Universal Declaration on the Human Genome and Human Rights (1997) UNESCO, available at: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html.

[333] Ruth Macklin, for example, is critical of the use of dignity in the Oviedo Convention: Macklin R (2003). Dignity is a useless concept *British Medical Journal* **327**: 1419–20. See also: Bagaric M and Allan J (2006) The vacuous concept of dignity *Journal of Human Rights* **5**: 257–70.

[334] It might not be necessary to await sufficient divergence that humans became incompatible as breeding partners: it is possible to imagine that human ingenuity might allow those with enriched genetic endowments to protect their advantage by introducing a genetic 'patch' that would prevent miscegenation with those who were comparatively genetically impoverished.

[335] Nietzsche F (1898) *Thus spake Zarathustra: a book for all and none.*

embodiment, human nature and human rights. For example, one group of scholars have been moved to propose a new international treaty to protect the 'endangered human':

> "*cloning and inheritable genetic alterations can be seen as crimes against humanity of a unique sort: they are techniques that can alter the essence of humanity itself (and thus threaten to change the foundation of human rights) by taking evolution into our own hands and directing it toward the development of a new species, sometimes termed the 'posthuman'.*"[336]

3.87 In making this proposal, they are reacting to the US political scientist, Francis Fukuyama. In his book *Our posthuman future*, Fukuyama argued that the possibility of changes to 'human nature' cannot be discounted given the unprecedented speed of development of the biosciences and the uncertainty of their effects. Fukuyama did not believe, however, that all people will be deterred from using genetic technologies by the safety risks and thought that, therefore, eugenic projects might emerge. Since "human nature is fundamental to our notions of justice, and the good life," he argued, "all of these will undergo change if this technology becomes widespread."[337]

3.88 The construction of this radical vision is, however, challenged by both empirical obstacles and theoretical objections. An empirical obstacle is the likelihood that uncontrolled population growth would swamp the outcome of any possible eugenic project.[338] A theoretical objection is that to ground human nature and the basis of human rights in a peculiarly evolved form of biological class of mammals is to radically misunderstand the conditions of possibility of human rights and unnecessarily to fall into an essentialist approach that may have some intuitively repugnant corollaries. The possession of 'human' rights need not entail a criterion of class membership rooted in the genome or, indeed, any other particular mode of description. Whereas the possession of a common genome offers certain opportunities for solidarity and altruism and a way in which we can identify with and help others, it is not the reason why we *should* do so. Our reasons for doing so spring from elsewhere.

Conclusions in relation to the humanity in general

3.89 The possibilities we have discussed in this section are admittedly far-fetched. Although requiring a degree of technical accomplishment that may or may not be possible at some time in the future, their present value is not as predictions, but as thought experiments to help orientate our reflections on what is important about the prospects of genome editing. From this we conclude that what is important is not the conservation or alteration of a particular range of characteristics at the level of the genome, but rather the potential consequences of genomic interventions for people and the social relations in which they stand to one another. These are expressed not in the pursuit of uncertain outcomes, but in the orientation towards those futures.

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[336] Annas GJ, Andrews LB, and Isasi RM (2002) Protecting the endangered human: toward an international treaty prohibiting cloning and inheritable alterations, *American Journal of Law and Medicine* **28**: 151–78. The 'crime against humanity' charge was in evidence in some responses to our refreshed *Call for evidence*; see, for example, response from Richard Hayes, PhD, Executive Director Emeritus, Center for Genetics and Society. In their response, Human Genetics Alert stated, "We would regard the creation of GM babies as a weapon of mass social destruction."

[337] Fukuyama F (2002) *Our posthuman future: consequences of the biotechnology revolution* (London: Profile Books). In fact, Fukuyama regards this worry (as expressed by the Council of Europe) as "a bit silly" (pp.78–9).

[338] In *Our posthuman future*, Fukuyama cites Fred Iklé. See: Iklé FC (2000) The deconstruction of death: the coming politics of biotechnology *The National Interest* 87–95.

3.90 Since we are using the concepts of human rights to address these questions, it has been important to consider whether or not the use of heritable genome editing interventions opens the possibility of undermining the basis of those rights. We have concluded that although particular interventions engage and may violate human rights, they do not threaten the basis of human rights as such. This is because entitlement to human rights does not depend on the possession of a 'human genome', even if such a thing could be described.[339] We are therefore left with the need to consider questions of the ethical use of genome editing on the basis of how they engage the intertwined rights and interests of individuals and in relation to the system of rights and the values that prevail in the societies in which they live.

General conclusion

3.91 In this chapter, we have explored three sets of considerations relating to heritable genome editing interventions, namely those relating to the individuals directly involved, those relating to others and the society in which they live and those relating to humans and human nature in general. Consistent with our understanding of heritable genome editing interventions as reproductive options set against a background of increasing genomic knowledge (Chapter 1) and the broader perspective on genome editing as a prospective technology that we developed in Chapter 2, we began by exploring the moral weight given to people's interests in having genetically related offspring with certain characteristics. We found that although they did not have a stand-alone positive right to assistance from others in this project, their interest was recognised as giving rise to moral claims of considerable force. Because of the peculiar nature of reproduction, whereby an intervention provided to one person has its primary effect on another (namely, a future person yet to be born), we examined the impact of heritable genome editing interventions with particular regard to how they might affect the identity and interests of the future person. We concluded that genome editing of gametes or embryos (or their precursors) would be morally permissible only when compatible with the welfare of a future person who may be born as a result. This includes cases in which there is an unacceptable risk of adverse effects of the procedure itself, and also where the selection is of the kind that might give the future person reasonable grounds to reprove their parents. We emphasise again that in the current state of knowledge, there are few complex characteristics that could be reliably secured by heritable genome editing interventions (i.e. that would be reliably expressed in the future person as a result of achievable genomic modifications). For this reason, while concerns about the safety of the procedure may be overcome, it is hard to foresee acceptable uses of heritable genome editing interventions other than as an alternative to existing procedures for the avoidance of heritable genetic disease or for the modification of alleles predisposing to disease risk.

3.92 Our second set of considerations place further constraints on the circumstances in which genome editing procedures may be used. These relate not to the interests of individuals directly involved, but to the interests of society and, in particular, to society's interest in safeguarding the indirect interests of people whose position in society may be made more vulnerable by genome editing technologies. It is recognised (as we observed in Chapter 2) that social norms do not remain constant and may be expected to change in relation to technological developments. Such changes should, however, come about in the context of broad societal debate that allows differences of values and interests to surface and to weigh. In the next chapter, we will consider in more detail the role that can be played by governance measures, including legal and regulatory measures, in

[339] On the coherence of this concept and its usefulness in governance, see Chapter 1 above and Chapter 4 below.

securing a publicly acceptable outcome whilst protecting individual rights and promoting social justice.

3.93 In the third part of the chapter, we considered whether there were any categorical limits to the use of genome editing technologies, such as introducing biologically unprecedented variations (rather than restoring a known 'wild type'). We concluded that if such experiments would not be biologically reckless and they would be consistent with the welfare of future people, not socially divisive and not initiated without prior societal debate, they would not necessarily undermine the concept of human rights or the rights of the future individual concerned. Given the present state of scientific knowledge, it is unlikely that any heritable genome editing procedure could satisfy these conditions in the near future.

3.94 We recognise that, in reaching these conclusions, we have given significant prominence to the interrogation of social norms in order to define current limits to what constitutes a good reason to select a particular kind of characteristic in one's future child. Those good reasons constitute, in effect, the public interest in developing and having genome editing technologies, which should inform public policy in this area. The production of this public interest as a social process creates the possibility of two kinds of marginalisation: the first is the marginalisation of values that diverge from the social norm within a given society; the second is the marginalisation of appreciation that accommodates different societal conclusions in a globalised world, creating ethical differences between different publics and different jurisdictions. These implications are addressed in the next chapter when we consider how conformity with the principles advanced in the present chapter can be better secured through practical legal and governance measures.

Chapter 4

Governance

Chapter 4 – Governance

Chapter 4 Overview

This chapter takes the conclusions arrived at in Chapter 3 and considers how the principles proposed could guide the formulation, amendment and application of practical governance arrangements, including legal, regulatory and professional governance measures.

The chapter reviews current legislation in the UK, Europe and internationally, as well as other significant jurisdictions (including the US and China), drawing attention to similarities and differences of approach. It identifies the different levels and scope of regulation and the challenges of a global situation in which the national legislation of different countries expresses different ethical values, but in which people, knowledge and skills are internationally mobile and where inequalities of wealth and access to technology persist. It draws attention to the human rights framework underpinning international law as providing a basis on which some elements relevant to heritable genome editing interventions could be further elaborated. It concludes that there is no prohibition in European community or international law that would make heritable genome editing interventions unlawful.

The chapter surveys UK legislation, noting that it currently prohibits heritable genome editing interventions. It also notes the richness of other forms of regulation and soft governance, including the role of learned and professional societies and institutions that contribute to fostering public debate and democratic participation.

The chapter makes concrete recommendations for research organisations in the natural and social sciences concerning, respectively, the development of standards of safety and clinical feasibility, and the investigation of the welfare implications of genome editing. Recommendations are made to the UK Government about the possible revision of current legislation to permit heritable genome editing interventions. The chapter makes clear that no move should be made to make heritable genome editing interventions lawful until there has been an opportunity for broad and inclusive societal debate, and it recommends the establishment of a new institution or commission to foster debate in this and related areas. Furthermore, any legislative change should be preceded by consultation with those who might be negatively affected and should not take effect until measures to monitor the social consequences and to mitigate any adverse effects are in place.

The chapter also makes recommendations to governments in the UK and elsewhere regarding the fostering of relevant public debate and the development of international human rights instruments to ensure a workable consistency of national approaches, accepting the need for margins of appreciation among members of the international community. States should, in particular, give consideration to ensuring that intellectual property rights are exercised in the public interest and that adequate protections against unfair discrimination are in place.

Finally, the chapter makes specific recommendations with regard to the regulation of heritable genome editing interventions, should their use be approved in the UK. These include that their use should not be permitted until risks of adverse outcomes have been thoroughly assessed, and then only on a case-by-case basis, licensed and regulated under the system currently overseen by the HFEA, and within the context of a carefully monitored study, with comprehensive follow-up arrangements in place.

Introduction

4.1 In the previous chapter, we considered the moral questions associated with heritable genome editing interventions. In this chapter, we will look at the suitability of current governance arrangements and how the conclusions in the previous chapter might inform the development of forward-looking arrangements. We will begin with the UK, although, as we have done throughout, we will also take into account situations in other nations and the global context. In so doing, we recognise that neither the practice of science or biomedicine, nor the authority of political communities is isolated from external moral, geopolitical or economic conditions. The question of international alignment, divergence and coordination will therefore be an important one.

National law and governance

The UK

4.2 The UK context is, in some ways, unusual compared to that of many other industrialised states. The existence of a nationalised health service since 1948 has largely insulated the UK from concerns about social justice and discrimination that have affected countries that rely on private insurance-based health and care provision. In relation to governance, too, the British 'regulatory state', in which the role of the independent regulatory agency rose to prominence, provided the UK with amenable (if not unproblematic) approaches to a number of public ethical problems.[340] This approach developed in the UK under both Conservative and Labour governments from the late 1970s onwards, during a period that saw several prominent bioethical issues emerge, while other states tended to adopt more rigid legal solutions or less accountable professional ones.[341] Despite these peculiarities, the UK nevertheless remains deeply and actively engaged in international processes and institutions; for example, as a member of the European Union and the Council of Europe and a member of the international community of nations instantiated in international organisations, including those of the United Nations.[342] The UK is often at the forefront of both scientific developments and ethical reflection internationally.

The Human Fertilisation and Embryology Act 1990 and the HFEA

4.3 The UK was one of the first states to develop formal governance arrangements in the field of assisted conception and human embryo research. These followed from the pioneering of *in vitro* fertilisation (IVF) techniques in England in the 1970s, which led to the birth of the world's first IVF baby in Oldham in 1978. Following that event, reproductive medicine practitioners established a Voluntary Licensing Authority (later the Interim Licensing Authority) pending the establishment of an independent, statutory

[340] Moran M (2002) Understanding the regulatory state *British Journal of Political Science* **32**: 391.

[341] This period saw a series of issues rising to public salience around which bioethical debate formed. These included genetically modified crops and the Human Genome Project, bookended by 'mad cow' disease and the first cloned sheep. The UK approach, which has been widely envied, if not emulated, was arguably enabled by a characteristically 'normal' distribution of British public opinion, the central mass of which has tended to be cautiously progressive in outlook given confidence in the probity of regulators.

[342] Following the national referendum in June 2016 that informed the UK Government's decision to serve notice under Article 50(2) of the Treaty on the European Union and thereby to trigger the withdrawal of the UK from the European Union, the termination of UK's formal membership of the European Union seems inevitable, although, at the time of writing, the nature and terms of its future relationship with the Union and other member states is still unclear and remains under negotiation. Independently of EU membership, the UK is also a member of the OECD, WEF, WTO, G7/G20, CBD and a number of other organisations, all fora in which geopolitical interests in genome editing have been explored.

regulatory system. The pioneering position of the UK research base in biology and biomedicine has meant that the UK has had to confront many ethical challenges before they arrive elsewhere, often having to invent new ways of doing so.[343] An early example was the establishment in 1982 of the Committee of Inquiry into Human Fertilisation and Embryology, which produced an influential report that led to the Human Fertilisation and Embryology Act 1990.[344]

4.4 The framework legislation provided by the Human Fertilisation and Embryology Act 1990 functions by statutory prohibition and qualified permission given through a licensing system. All uses of gametes and embryos outside the body are prohibited unless carried out in pursuance of a licence and subject to oversight by the regulator, the Human Fertilisation and Embryology Authority (HFEA).[345] Licences can authorise research using gametes or embryos (including both supernumerary embryos donated by those undergoing IVF procedures and embryos created specifically for research). To be licensed, such research must be found to be 'necessary or desirable' for one or more of a number of purposes specified in the Act.[346] Since the Act specifies the purposes for which research may be carried out rather than the procedure used, genome editing techniques may be regarded as merely another tool in the researcher's toolbox provided their proposed use falls within the approved statutory purposes.[347] The Act also prohibits the conduct of research on embryos after a period of 14 days beginning with the day on which the process of creating the embryo began.[348] As noted in Chapter 2, genome editing research beyond day 14 has the potential to advance understanding of congenital disease, so this constraint may appear less justifiable as research advances.[349]

4.5 The HFEA also licenses all clinical fertility treatments involving gametes and embryos. (In most cases, centres are licensed to perform a stated range of licensable treatments, although in some – more controversial – cases, the treatments are licensed on a 'named patient' basis.[350]) Certain activities cannot be licensed and are therefore subject to an absolute legislative prohibition. Activities that cannot be licensed include using a gamete or an embryo in treatment that is not a 'permitted' gamete or embryo as defined in the Act.[351] Any gamete or embryo that has been subject to the genome editing procedures discussed in this report is not, at the time of writing, a 'permitted' gamete or embryo.[352]

4.6 The effect of current legislation to prohibit the use of edited gametes or embryos in treatment could nevertheless be overcome by amending the definition of a 'permitted'

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[343] See: Leather S and Mills PFR (2005) Regulation of assisted reproductive technology: the UK experience – themes and trends, in *A textbook of in vitro fertilization and assisted reproduction: the Bourn Hall guide to clinical and laboratory practice,* 3rd ed., P Brinsden (Editor) (Boca Raton: CRC Press), pp.623–31.

[344] *Report of the Committee of Inquiry into Human Reproduction & Embryology* (the 'Warnock Report') 1984 (Cmnd 9314) (London: HMSO).

[345] Fresh, unprocessed partner sperm for use in treatment is exempted and some non-reproductive uses of gametes are generically exempted from specific licensing by regulations. There are essentially five licensable activities (keeping and using gametes and creating, keeping and using embryos), but the licensing regime gives significant discretion to the HFEA to impose conditions on how those activities may be carried out, giving the HFEA flexible and potentially wide-ranging control over a large range of activities and the ability to respond to developments in technology.

[346] Human Fertilisation and Embryology Act 1990, Sched.2, para.3A(2).

[347] Indeed, there is no reason on the face of the legislation to expect the HFEA to know whether a licensee is using genome editing techniques in their research. The HFEA has the power to place reasonable conditions on a licence that might restrict this or make relevant provision in its *Code of practice*. So far, the Authority has licensed one research project that involves genome editing applied to human embryos – at the Francis Crick Institute in London – which attracted significant public attention.

[348] Human Fertilisation and Embryology Act 1990, s.3.

[349] On this question, see: Nuffield Council on Bioethics (2017) *Human embryo culture, discussions concerning the statutory time limit for maintaining human embryo in culture in the light of some recent scientific developments,* available at: http://nuffieldbioethics.org/project/workshop-time-limits-maintaining-human-embryos-research.

[350] This is the case for treatments involving preimplantation genetic diagnosis with tissue typing and for mitochondrial donation.

[351] HFE Act 1990 (as amended), s.3(2).

[352] HFE Act 1990 (as amended), s.3ZA.

gamete or embryo. The capacity to do so was built into the Act in 2008 in response to promising developments at the time in cell reconstruction techniques for the avoidance of mitochondrial disease.[353] These provided that future regulations governing the therapeutic application of donated mitochondria 'to prevent the transmission of serious mitochondrial disease' could make an egg or embryo that had been subjected to 'prescribed processes' carried out 'in prescribed circumstances' a 'permitted' egg or embryo. This allowed Parliament to pass Regulations in 2015 to that effect, following a number of expert reviews, public engagement initiatives and sustained deliberation (including by the Nuffield Council on Bioethics), culminating in debates on the floor of both houses of Parliament.[354] The regulation-making power introduced in 2008 is, however, highly constrained, permitting regulations only very limited scope. While it could arguably be used to extend the 'prescribed processes' under the 2015 Regulations so as to allow an embryo that has been subject to genome editing to be used in treatment, the purpose would remain limited by the Act to preventing 'the transmission of serious mitochondrial disease'. For any other purpose, it would therefore be necessary to revisit the primary legislation.[355]

4.7 In passing the 2015 Regulations, the UK has both broached and answered a question that has been a focus of controversy in bioethics at least since the development of recombinant DNA technologies in the 1970s: that of the permissibility of human 'germ line' modification. By passing the 2015 Regulations, the UK Parliament has approved the practice of making deliberate biological changes that may be inherited by future generations. Nevertheless, while it was acknowledged in the parliamentary debates that 'germ line modification' was to be made legally permissible, it was simultaneously denied that these procedures amounted to 'genetic modification'. The basis of this denial was that, in mitochondrial donation, the modification would be at the level of substituting whole subcellular structures (pronuclei or maternal spindles), rather than deliberately altering the sequence of bases comprising any DNA molecule.[356] This approach implicitly

[353] Section 3ZA(5).

[354] The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (S.I 2015 No. 572). See also: 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.The first treatment licence was issued by the HFEA in early 2017.

[355] According to the Act, 'permitted' sperm, eggs and embryos (i.e. those that may be used in treatment) are subsets of those things meant by 'sperm', etc., according to section 1 of the Act (including those things that are capable of being meant by 'sperm', etc., pursuant to any Regulations that may be made under section 1(6)). This 'permitted' subset has specific conditions (at paragraphs (a) and (b) of subsections (2) and (3), and paragraphs (a), (b) and (c) of subsection (4) of section 3ZA for eggs, sperm and embryos, respectively). These conditions can be disapplied in the case of eggs and embryos as prescribed by Regulations under section 3ZA(5). The Regulations must follow the 'affirmative resolution' procedure, requiring that they be laid before and approved by both houses of Parliament. However, the cases in which this can happen (i.e. in which eggs or embryos that do not satisfy the conditions in section 3ZA(2) or (4), respectively, may be used) are explicitly limited (by section 3ZA(5)) to the avoidance of the transmission of serious mitochondrial disease. For this purpose, *and for this purpose only*, the use of various experimental cell types could be prescribed in Regulations if any or all of the conditions in section 3ZA(2) and/or (4) were disapplied and those cell types were brought within the meaning of 'eggs' and 'embryos' by section 1(6). These might include, for example, stem cell-derived eggs, reconstructed and genetically modified eggs or embryos created by various cloning and reconstruction procedures. Interestingly, while the use of reconstructed or genetically modified eggs and embryos can be authorised by Regulations, in the case of an embryo, the sperm that contributes to it cannot be (thus, stem cell-derived eggs could be used, but only if fertilised with sperm taken from a man and not genetically modified). In view of potential technical developments, we have identified (see our discussion in Chapter 2) the difference between allowing the use of some cell types to avoid a limited range of diseases to be authorised by Regulations and requiring that the use of other cell types for the avoidance of all other diseases to be authorised by primary legislation, though historically explicable, now seems arbitrary and irrational.

[356] In debates, the Government adopted a 'working definition' of genetic modification: "The working definition adopted by the Government for the purpose of taking forward the Mitochondrial Donation regulations states that genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations. Mitochondrial donation is not considered to be genetic modification, as the patient's nuclear DNA remains unaltered during this process." Change to HL Hansard (5 February 2015) Written statements and written answers, pp.11–12, available at:

distinguishes two thresholds at which permission might be held up: at the cellular level (the Rubicon that was crossed in the case of mitochondrial donation) and at the molecular level (the current frontier).

4.8 There is something odd and potentially unstable about the UK's approach, however. It has sought to draw a line between, on the one hand, cell reconstruction involving specific instances of genetic material from distinct lineages, which will functionally interact in the resulting person, and, on the other, targeted genetic modification that might, for example, 'correct' a single-base mutation. It has furthermore unusually singled out a particular class of diseases (serious mitochondrial diseases) in this way, making that class of diseases the only one for which germ line modification procedures may be carried out. (The substitution techniques laboriously provided for in the 2015 Regulations would have little use other than in cases of serious mitochondrial disease – although they have been used elsewhere in the world for purposes of overcoming infertility.[357] On its face, however, the power in the Act could be used to make Regulations that would permit 'genetic modification' of nuclear DNA, which could have a much wider range of uses, were it not restricted to preventing the transmission of mitochondrial diseases.)

4.9 Furthermore, there is one very specific case where intergenerational genome editing might be accomplished that does not appear to be caught by the Human Fertilisation and Embryology Act 1990. This is the case we described in Chapter 2 in which diploid sperm precursor cells (spermatogonia) are retrieved from a patient, edited *in vitro* using a genome editing technique such as the CRISPR-Cas9 system and returned to the patient's testes (which may have been sterilised in the meantime to destroy any wild-type sperm and sperm precursors).[358] If sperm production (spermatogenesis) were completed in the testes from these edited spermatogonia, this would, in theory, enable the patient to conceive a child with a partner through unassisted conception, with the result that the alteration could be transmitted via the sperm to the offspring. The reason this would not be caught by the regime of the Act is that none of the procedures contemplated involves a licensable activity within the meaning of the Act.[359] This is not to say that the therapy to which the male would be subjected, as distinct from its reproductive consequences, would be entirely unregulated, at least in Europe. In common with other autologous uses of human tissues (and HFEA-regulated treatments), the editing and transplantation procedure would be governed by national quality and safety legislation implementing the EU Tissues and Cells Directive, which concerns the quality, safety and traceability of cells used for human application.[360] However, it is questionable whether the autologous graft would be regulated as a marketed medicine by falling under Advanced Therapy Medicinal Products (ATMP) Regulation.[361] Regulators might argue that the re-implanted cells are susceptible to the ATMP

https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Lords/2015-01-22/HL4366/.

[357] See, for example,: New Scientist (18 January 2017) First baby born using 3-parent technique to treat infertility, available at: https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/.

[358] As indicated in Chapter 2, this might also be accomplished using gametes originated in edited induced pluripotent stem cell lines differentiated into spermatogonia before engrafting.

[359] The question becomes interesting if the sperm are used in licensed assisted conception. While section 1(4)(b) provides that "references to sperm are to live human sperm, including cells of the male germ line at any stage of maturity," the actual cells that are engrafted would not themselves have had to be altered (they would be the daughters or more remote descendants of altered cells) and may not, therefore, fall foul of section 3ZA(3)(b) – although we concede that the HFEA would be bound to argue that they do – particularly if the elements of subparagraphs (a) and (b) are thought of as sequential in the case in which the edited spermatogonia have been engrafted into a testis.

[360] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004L0023.

[361] Regulation EC 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004, available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32007R1394.

Regulation, and point to the fact that most ATMP marketing approvals are for autologous products. However, the fiction that they are placed on a market is not compelling, and cases would probably fall under the 'special exemption' to the Medicinal Products Directive, or the 'hospital use' exemption under the ATMP Regulation. Despite this, the engrafted product would remain subject to good manufacturing practice requirements and to the laws of negligence and product liability (as regards the implanted seminiferous tissue). No other regulatory control would apply to the edited, engrafted spermatogonia themselves, however, and we suggest that such control might be problematic, in any case, for human rights reasons elaborated elsewhere in this chapter.

4.10 Fertilisation using edited spermatozoa potentially offers benefits over *in vitro* editing of embryos, particularly if they can be derived from stem cells where there is the opportunity to undertake prior quality control measures, leading to a lower risk of off-target effects and mosaicism in the resulting embryos. On the other hand, it has intrinsic limitations, as it offers editorial control over only half of the genetic endowment. Although it is theoretically interesting, and the key elements (except the editing step) have already been demonstrated in primates, it may not be a procedure of first choice (especially, perhaps, if there were a requirement irreversibly to sterilize the male partner). Nevertheless, it is potentially a shortcoming that the only regulatory regimes by which it would be caught are primarily orientated towards the protection of patients, do not contemplate cell therapies involving germ cells (or induced pluripotent stem (iPS) cell equivalents) and do not involve crucial elements that are only partly present in the UK's human fertilisation and embryology regime, but which we believe are particularly important to the interests of future individuals born as a result of editing interventions, and of society more generally.

Regulation, compliance and public confidence

4.11 Under the Human Fertilisation and Embryology Act 1990, reproductive biomedicine in the UK is controlled at three separate levels: through statutory provisions that distinguish those things that are prohibited absolutely (and subject to criminal penalties) and those things that are permissible under licence; through the licensing regime that allows the HFEA to determine what licensable activities may be carried out, by whom and in what circumstances; and through the HFEA's oversight of clinics, which ensures that the licensable activities are carried out in accordance with licence conditions and in conformity with the Authority's statutory *Code of practice*.[362] The legislation also gives the HFEA a triple hold on the conduct of licensed activities, first in relation to the kind of *cells* involved (gametes and embryos), second in relation to the kind of *activities* carried out (creating, keeping, using) and third in relation to the *purposes* for which those practices involving those cells are carried out (treatment services or the scheduled research purposes).[363] It should be noted here that among the measures that currently

[362] Under section 25 of the Human Fertilisation and Embryology Act 1990 (as amended), the Authority is required to maintain a *Code of practice* giving guidance on the proper conduct of licensed activities and the proper discharge of the functions of the person responsible and other persons acting in pursuance of a licence. The Authority has an inspection function and, in considering whether to grant or revoke a licence, a licence committee is entitled to take into account compliance with any provision of the *Code of practice*. The extent to which the *Code of practice* mechanism has been used to enforce certain behaviours has varied over the history of the HFEA. An example of regulatory activism is the elaboration, in successive versions of the *Code of practice*, of what is expected of clinics in taking account of the 'welfare of the child' who may be born as a result of treatment (a statutory licence condition applied by section 13(5) of the Act, itself amended in 2008).

[363] 'Treatment services' are defined in section 2 of the Act as "medical, surgical or obstetric services provided to the public or a section of the public for the purpose of assisting women to carry children" (although not all treatment services are licensable or otherwise prohibited), and research purposes are set out in Schedule 2, paragraph 3A(2).

function on the third level of HFEA control is the requirement, stipulated as a condition of all treatment licences by section 13(5) of the Act, that "a woman shall not be provided with treatment services unless account has been taken of the welfare of any child who may be born as a result of the treatment (including the need of that child for supportive parenting), and of any other child who may be affected by the birth."[364]

4.12 Although the HFEA has significant powers of enforcement and sanction, compliance with the basic legal constraints has tended to be high and good practice is very well embedded in the sector.[365] This may be partly attributed to the way in which the sector has grown out of a well-organised cadre of practitioners, socialised through medical training and specialism, whose leaders are typically members of a Royal College (the Royal College of Obstetricians and Gynaecologists) and professional membership organisations (the British Fertility Society, the British Andrology Society and the Association of Clinical Embryologists). Reciprocally, elite members of these organisations have been closely involved in governance making (e.g. through membership of the HFEA's board and committees and through setting professional standards). The field has also enjoyed a large measure of cautiously progressive public support (e.g. in relation to donor conception, embryo research, etc.) that rests on a tradition of high-quality debate in the public sphere going back to the Warnock Committee and carried on more recently in Parliament and its Select Committees, through the activities of charitable organisations like the Progress Educational Trust, specific public engagement around various policy initiatives and the hawk-like media attention given to issues in reproductive biomedicine.[366]

Other legal and governance cultures

4.13 We have noted that the UK's approach to human biotechnology governance is distinctive in many ways, largely due to its regulatory system for assisted reproduction and human embryo research. The UK exists, however, within an international context that includes countries with very different legal, religious, cultural, political and philosophical traditions, among which there are inequalities of wealth, infrastructure and civil liberties, and between which there are movements of knowledge, skills, technologies, tissues, patients and data. Many of these countries have active research programmes involving genome editing, although not all permit research on human reproductive cells and particularly human embryos.[367] Countries that have legislation or other formal governance mechanisms in place have sought to control the kinds of intergenerational genome editing discussed in this report in a number of ways.[368] It should be remembered, however, that there are also countries that have no (or very little) applicable legislation

[364] Human Fertilisation and Embryology Act 1990 (as amended), s.13(5).

[365] The HFEA has not had to deal on very many occasions with clinics breaking the law, but has often had to deal with practices that rub away at the margins of acceptability, often for the clinic's competitive advantage (e.g. transferring multiple embryos, selling add-ons of unproven clinical value, circumventing prohibition on payment to gamete donors, etc.). For recent non-compliance reporting, see the section on 'Non-compliances found on inspection' at p.17ff: https://www.hfea.gov.uk/media/2437/hfea_state_of_the_sector_report_tagged.pdf.

[366] At crucial moments, these have been bolstered by the intervention of patient groups (e.g. in relation to the HFE (Research Purposes) Regulations 2001 (S.I. 2001, No. 188) that, in effect, paved the way for human embryonic stem cell research. Groups opposed in principle to certain assisted conception procedures (such as Comment on Reproductive Ethics) have also played a role in ensuring the probity of the sector and its regulator, often through legal action (see *Quintavalle (on behalf of Comment on Reproductive Ethics) v. Human Fertilisation and Embryology Authority* [2005] UKHL 28).

[367] The most prolific countries for research publications citing CRISPR, for example, are the US, China, Japan and Germany; see: https://www.elsevier.com/research-intelligence/campaigns/crispr.

[368] See: 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; Isasi R, Kleiderman E, and Knoppers BM (2016) Genetic technology regulation: editing policy to fit the genome? *Science* **351(6271)**: 337–9.

or other effective measures that would allow control of heritable genome editing interventions.

Europe

4.14 In Europe, despite the existence of established and well-respected supranational and international institutions such as those of the European Union and the Council of Europe, there is a mixture of formal legal prohibitions (particularly in civil law countries) and administrative guidelines among European countries. The extent to which these may have been drafted with particular technologies or approaches in mind, and therefore the extent to which they should apply to genome editing technologies, is, in some cases, ambiguous. There is also a plurality of governance cultures, some centralised in government ministries, some (like the UK) with established, independent regulatory agencies and others relying on professional organisations and professional ethics. Some countries prohibit any use of human embryos in research or only permit research that is supposedly 'for the benefit of the embryo'. Italy falls into this latter category.[369] Others that permit embryo research, such as Sweden, prohibit heritable genetic modification of human embryos, though it is ambiguous whether this would make it unlawful to modify embryos for research purposes.[370] The majority of states that permit embryo research only allow research on supernumerary IVF embryos and prohibit the creation of embryos specifically for research (the UK being among a small number of outliers in this respect).[371] While many countries permit the selection of embryos to avoid certain genetic conditions associated with disease or disability (i.e. preimplantation genetic testing) in treatment, most have strict laws and guidance relating to the conditions for which this is permissible.

4.15 The extent to which ethical foundations of human rights are articulated explicitly in legal provisions varies. Many Western European civil law countries explicitly acknowledge values such as human dignity as the foundation and principle of their ethical laws. In Germany, for example, the Basic Law (*Grundgesetz*), in its first Article, states that "Human dignity shall be inviolable," and that "To respect and protect it shall be the duty of all state authority explicitly." It carries on much in this vein.[372] Germany's 1990 Embryo Protection Act also starts by making it clear that the proper use of assisted reproduction technologies is for bringing about a pregnancy.[373] Preimplantation testing is strictly controlled and limited, and criminal penalties apply to any attempt to alter the genetic information of a human germ line cell artificially (except for research) or to use a human gamete with artificially altered genetic information for fertilisation.[374]

Other civil law jurisdictions

4.16 Japan's non-binding 2002 Guidelines on Gene Therapy Clinical Research prohibit "Gene therapy clinical research aimed at, or that may cause, genetic modification of human

[369] Repubblica Italiana 2004 Legge 19 Febbraio 2004. Norme in materia di procreazione assistita. Gazzetta Ufficiale della Repubblica Italiana. Serie generale 45, 5–12, available at: http://www.gazzettaufficiale.it/eli/gu/2004/02/24/45/sg/pdf.
[370] The Swedish National Council on Medical Ethics (2002) *Statement of opinion on embryonic stem cell research*, available at: http://www.smer.se/publications/statement-of-opinion-on-embryonic-stem-cell-research/.
[371] Belgium and Israel are also among the countries that allow the creation of embryos for research.
[372] German Basic Law (Grundgesetz), Art. 1(1).
[373] Embryo Protection Act 1990 (Gesetz zum Schutz von Embryonen/Embryonenschutzgesetz – EschG).
[374] Embryo Protection Act 1990, s.5. Despite this, there is concern that potential loopholes might allow germ line therapies that would support the life and integrity of an embryo.

germ cells or embryos."[375] The Council for Science, Technology and Innovation at the Japanese Prime Minister's Office is, however, reported to be considering a revision of Japanese policy set out in the draft Comprehensive Strategy on Science, Technology and Innovation, as well as adopting regulations on embryo research to restrict human embryo modification through genome editing to basic research, while prohibiting the transfer of edited embryos.[376]

4.17 Civil law approaches to governing areas of rapid technological change may offer less flexibility or leave a lot of work to be done through guidelines and interpretation at regional level rather than common law systems. Mexico (The United Mexican States) is a civil law jurisdiction (albeit structurally quite similar to the US) and, like China, there are disconnections in practice between Federal Law and regional practice (conservatives and progressives continue to argue over the protections afforded to embryonic human life by the federal constitution).[377] This situation, and its geographical convenience, combined with its slowness in passing new legislation, probably contributed to the decision to carry out the first reported transfer of an embryo reconstructed using the maternal spindle transfer technique to avoid mitochondrial disease in Mexico, a procedure that would have been unlawful in the US where the embryo was actually reconstructed.[378]

Other common law jurisdictions

4.18 The Israeli Law on the Prohibition of Genetic Intervention prohibits "[u]sing reproductive cells that have undergone a permanent intentional genetic modification (Germ Line Gene Therapy) in order to cause the creation of a person." This is in view, explicitly, of the 'implications for human dignity', among other things, although, on the recommendation of the advisory committee, the Minister has the power to override this prohibition "if he is of the opinion that human dignity will not be prejudiced."[379] Human dignity also underwrites the right to family life, which has been interpreted as enjoining a "positive aspect [that] goes to the state's duty to assist the individual in exercising the right."[380]

4.19 India, which adopted its common law system from Britain, does not prohibit genome editing explicitly, but its historical difficulties in controlling sex selection means that it controls prenatal (including preimplantation) diagnostic testing for a list of conditions that may be expanded by the Central Supervisory Board.[381] The Council of Medical Research's Ethical Guidelines for Biomedical Research on Human Subjects bans germ line therapy "under the present state of knowledge" and "for selection against personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics" or to enhance offspring beyond the normal range.[382] The Council also issued National Guidelines for Stem Cell Research, which contain a

[375] Japan Guidelines on Gene Therapy Clinical Research 2002 (as amended 2008), s.6.
[376] See: http://japan.kantei.go.jp/97_abe/actions/201605/13article1.html.
[377] Article 1 of the Constitution provides: "Any discrimination based on ethnic or national origin, gender, age, disabilities, social status, health condition… or any other reason which attempts against human dignity and which is directed to either cancel or undermine people's rights and liberties is prohibited." See: Palacios-González C and Medina-Arellano M (2017) Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case *Journal of Law and the Biosciences* **4(1)**: 50–69.
[378] Palacios-González C and Medina-Arellano M (2017) Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case *Journal of Law and the Biosciences* **4(1)**: 50–69.
[379] Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law 5759-1999, Art.3(2) (prohibition) and Art.5(a) (exception).
[380] *Moshe v. Board for Approval of Embryo Carrying Agreements under the Embryo Carrying Agreements Law* (Approval of the Agreement and the Status of the Child) 5756-1996 HCJ 5771/12 (Israel, like the UK, is a common law country).
[381] Pre-Conception and Pre-Natal Diagnostic Techniques Act 1994 (as amended 2002), s.4(2).
[382] Chapter IV, s.(ii)–(iv).

prohibition on culturing genome-modified human embryos beyond 14 days after fertilisation or the formation of the primitive streak, as well as research related to human germ line gene therapy. The guidelines also prohibit the use of genome-modified human embryos, germ line stem cells or gametes for developmental propagation and research involving implantation of human embryos after *in vitro* manipulation into humans or primates.[383]

4.20 The distinction between civil law and common law jurisdictions is perhaps less important, however, than national political and governance cultures, which are usually a function of the level of integration, communication and homogeneity across the professions, administrators and regulators, the salience of biomedicine in the public sphere and the significance and cohesiveness of the public sphere itself. Two countries, which differ greatly according to these measures, tower over the rest with regard to research output on basic genome editing research and are therefore potential destinations for research and reproductive tourism.

United States of America

4.21 To date, the most prolific country by far with regard to 'basic' genome editing research is the US.[384] The fact that this is possible in a country with deep and immobilising moral division between liberalism and Christian fundamentalism, and steeped in permanent conflict over abortion rights that has effectively evacuated any middle ground on which to build a societal consensus, may be attributed to the US constitution and its defence of civil rights and liberties. The US has, internationally, the largest federal research budget and, though this cannot currently be used to fund research in which human embryos are "destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research of fetuses *in utero*," it has equally surpassing quantities of private funding, which allows research to progress at pace, despite a strong domestic anti-abortion lobby.[385]

4.22 Francis Collins, Director of the National Institutes of Health (NIH), which funds health research in the US, was quick to issue a statement affirming that the NIH "would not fund any use of gene-editing technologies in human embryos."[386] (The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (2016) state that "The NIH will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer"[387]). Nevertheless, the organising committee of a international summit hosted by the National Academies of Sciences and co-organised with the UK Royal Society and the Chinese Academy of Sciences

[383] National Guidelines for Stem Cell Research, Indian Council for Medical Research and Department for Biotechnology (July 2017), available at: https://icmr.nic.in/guidelines/guidelines_for_stem_cell_research_2017.pdf. s. 9.2.8.3 and s.9.3.

[384] The reference here is to laboratory research, largely in other animal models, although with notable published research on human embryos; see, however, Chapter 2 above on the significance and instability of the distinction between 'basic' and 'applied' or 'clinical' research.

[385] Omnibus Appropriations Act, 2009 (Dickey–Wicker Amendment, 1996), Sec. 509(a).

[386] See: Nuff' said blog (30 April 2015) NIH throws out the bathwater, baby and all, available at: http://nuffieldbioethics.org/blog/nih-throws-bathwater-baby.

[387] The NIH continues to explore the issues raised by the potential of *in utero* gene transfer clinical research; however, it has concluded that, at present, it is premature to undertake any *in utero* gene transfer clinical trial pending significant additional preclinical and clinical studies and understanding of the development of human organ systems, such as the immune and nervous systems; see: NIH (2016) *Guidelines for research involving recombinant or synthetic nucleic acid molecules*, available at: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html.

published a statement later that year calling for responsible research in this area, but stopping short of endorsing any move into clinical use.[388]

4.23 The National Academy of Sciences (NAS) and the National Academy of Medicine (NAM) subsequently produced a report in February 2017 recommending the use of existing regulatory infrastructure and processes to evaluate future basic laboratory research on genome editing and somatic gene therapy involving genome editing.[389] However, the report also foresees the possibility of 'germ line' applications in clinical trials for 'compelling reasons' once risk–benefit questions have been more carefully addressed.[390] While the report finds the social consequences of genome editing to be an important consideration, it tends to suggest that use of genome editing will remain rare and exceptional. It also affirms the need for broad public engagement, although this is largely limited to 'input' into decisions about when the technology should be used.[391] As the authors of the report were well aware, however, early trials were unlikely to take place in the US owing to the congressional stand-off. Under the Public Health Service Act and the Federal Food, Cosmetic and Drug Act, the US Food and Drug Administration (FDA) has the authority to regulate products and drugs involving genome editing, including human genome editing, at the federal level (the FDA has already asserted its competence to regulate human genome editing in this way).[392] Owing to an appropriations bill rider, however, the FDA is prevented from using its resources to convene a committee to consider an application, with the result that no applications can be approved.[393]

China

4.24 China is second only to the US in terms of its output of 'basic' research papers on genome editing and is more prolific in research on human embryos (it was the source of the first three papers reporting genome editing in human embryos). The context of research and assisted conception treatment in China is, however, very different from that in the US. Whereas the US has found oblique but constitutionally effective ways of variously circumventing and reinforcing public moral division over the status of the human preimplantation embryo that is never far from the surface, these challenges have been largely absent in China. While at the public level China has moved towards embracing international human rights, it has sought to meld this with traditional Confucianism, in which moral status is entailed by the acquisition of personhood, which begins at a child's birth (rather than at the time of conception) and develops gradually

[388] See: 'On human gene editing: international summit statement', available at: http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a.

[389] National Academies of Sciences, Engineering, and Medicine (2017) Human genome editing: science, ethics, and governance, available at: https://doi.org/10.17226/24623.

[390] It also foresees the use of somatic genome editing for 'enhancement' purposes in the future, but recognises that the liminal questions about health and enhancement are difficult to answer.

[391] Philosopher and bioethicist, Françoise Baylis, who was a member of the organising committee for the 2015 Washington summit, observes that slippage between the summit's lofty call for international dialogue and a gesture towards ''the public' in the later report, as well as an implicit acceptance of clinical use for some purposes: "In this way, the answer to the original question of 'who' has been made opaque and the original question of 'what' has been transformed from a question about the moral demarcation line between somatic gene editing and germline gene editing to a question about the moral demarcation line between germline gene editing for therapeutic purposes and germline gene editing for enhancement purposes." Baylis F (2017) Broad societal consensus on human germline genome editing, *Nature Human Behaviour* **1**, 0103.

[392] See US Food and Drug Administration (2018) Therapeutic cloning and genome modification, available at: https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm2007205.htm.

[393] Public Law 115–141 Consolidated Appropriations Act, 2018, Section 734, available at: https://www.congress.gov/115/bills/hr1625/BILLS-115hr1625enr.pdf. As the rider has to be renewed every year, its removal could be achieved simply by a failure to do so, which would then allow the FDA to receive applications to conduct germ line genome editing trials. However, the stand-off has so far proved irresolvable. Such apparently oblique mechanisms are a common feature of US politics and legislation.

through social practice.[394] Consequently, traditional Chinese culture is, by international standards, relatively hospitable to responsible human embryo research.[395] It should be remembered that China has pursued population control as a public policy objective and, until 2015, strongly discouraged multiple-child families.[396] Alongside this, the Chinese government has attached great importance to preventing the transmission of genetic conditions and actively encouraged the use of PGT as well as other forms of preconception and prenatal screening.

4.25 Governance of biomedical research and practice in China is centralised under the National Health and Family Planning Commission (NHFPC), which is responsible for laws, regulations, policies and plans related to public health, including the ethical governance of biomedical research and applications. It oversees medical practice in state hospitals and medical institutions and is also responsible for population control and family planning. Genome editing research on human embryos is permitted and subject to a number of relevant guidelines. However, Articles 3.7 and 3.9 of the 2003 'Technical Norms of Human Assisted Reproductive Technologies' provide that "gene manipulation on human gametes, zygotes and embryos for the purpose of reproduction is banned."[397] Although these standards have the legal status of a ministerial guideline, assisted conception clinics in China are regulated by the NHFPC, which shut down a large number of unapproved IVF clinics in the mid-2000s. Despite this, driven by the large profits to be made from growing demand for assisted reproductive technology (ART) services, a number of unauthorised private clinics have reappeared in recent years, despite the risk of punishment, and hence reproductive services such as sex selection and surrogacy, which are technically illegal in China, are nevertheless available in practice.[398]

4.26 While China has clear formal guidelines, the implementation of China's legal and regulatory system for ARTs and human embryo, gamete and germ line genome editing research has proved difficult in practice. In a background report commissioned by the Nuffield Council to support this project, Achim Rosemann, Li Jiang and Xinqing Zhang identify five factors that help explain this.[399] These are, first, China's large territory, huge proliferation of research institutes and limited communication infrastructure; second, the dispersal of the regulatory oversight of healthcare and biomedical research among a large number of government departments and agencies with limited integration; third, the

[394] See: Hui EC (2003) Personhood and bioethics: a Chinese perspective, in *Bioethics: Asian perspectives*. Dordrecht: Springer Netherlands, pp.29–43, cited in Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics).

[395] Cong YL (2008) From Chinese values of life to exploring the ethical aspects of stem cell research in mainland China *Contemporary Chinese Thought* **39(2)**: 18–31, cited in Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics).

[396] The move to a 'two-child policy' in late 2015 has boosted the market for prenatal genetic screening and testing: see Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics).

[397] Controls may be specified at three levels in China: by laws, regulations and ministerial guidelines. Of these, ministerial guidelines are the most relevant, although they are enforceable only if mentioned in a law, regulation or administrative measure. They include administrative measures, ethical guidelines and principles and technical norms and standards. See: Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics); see also: Ishii T (2015) Germline genome-editing research and its socioethical implications *Trends in molecular medicine* **21(8)**: 473–81.

[398] Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics)

[399] ibid.

fact that national regulations offer only general guidance while implementation is left to government departments at a provincial level, leading to substantial variation; fourth, the parallel system of military and police universities, research institutes and hospitals, which have regulatory bodies and rules that are distinct from those of civil institutions and which typically allow a greater level of freedom (e.g. enabling for-profit research arrangements that would be prohibited in state hospitals)[400]; and fifth, scientists and regulators consider the adoption and implementation of stringent regulatory norms to be an obstacle for innovation, limiting local research and economic opportunities.

4.27 Encouraged by international competition and given its Confucian traditions, China appears to be a candidate to lift the ban on intergenerational genome editing if sufficient evidence were adduced to support a move into clinical use. On the other hand, in the context of the difficulties of regulatory implementation, there is a history of clinics in China offering premature, illegal and sometimes highly risky clinical innovations (such as stem cell therapies). This inevitably gives cause for concern in relation to heritable genome editing interventions, although premature innovation would likely precipitate rapid and decisive action on the part of Chinese regulators.[401]

4.28 Unlike the US, where debate is open and fierce, if lacking in focus, or like the UK, where debate tends to be more coherently orientated towards regulatory or parliamentary activities, there is (at least up to the end of 2017) little public and media debate in China that allows space for diverse stakeholders and points of view, and no evidence of public engagement initiatives, either on the part of government-related bodies or civil societal organisations. Official science communication appears overly politicised, although some Chinese scientists pursue a "calculative balance of observing and subverting institutional constraints" to circumvent this.[402] A platform for uninvited debate is offered by the microblogosphere, although due to strict internet censorship, possibilities for political activism remain limited. Investigation of comments on websites and journals suggests some support for human genome editing under careful ethical and regulatory scrutiny.[403]

The problem of geo-ethics

4.29 The distinction between civil law and common law jurisdictions and between legal provision and guidelines is perhaps less important for the governance of emerging biomedical technologies than how the measures in use fit with local political culture and the way that societal interests are constituted and engaged. To take just one example, it would be extremely difficult, given the moral divisions in US society over abortion, to implement the kind of regulatory solution (particularly one that benefits from periodic engagement with public) that is currently in effect in the UK.[404] In states with a unifying national ethos, such as Singapore, South Korea or Nordic countries, governance can shape research and innovation more closely than in regionally and socially diverse states, like the US and China, where a range of activities often goes on despite the apparent comprehensiveness of governance arrangements. In other words, in larger political associations, there can be less coherence between the superficially

[400] ibid.
[401] ibid., at p.40. China has certainly forged ahead with clinical trials of somatic genome editing therapies: see https://www.wsj.com/articles/china-unhampered-by-rules-races-ahead-in-gene-editing-trials-1516562360.
[402] See: Zhang J (2015) The 'credibility paradox' in China's science communication: Views from scientific practitioners *Public Understanding of Science* **24(8)**: 913–27.
[403] See: Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics).
[404] This was explored by the US President's Council on Bioethics in 2002; see: https://bioethicsarchive.georgetown.edu/pcbe/transcripts/oct02/oct18.html.

comprehensive arrangements and the deep currents of practice than in smaller or more homogeneous ones.

4.30 At an international scale, the divergence between the superficial overlay of international law and local practice is radically exacerbated. The globalisation of neoliberal capitalism has created the conditions not only for greater possibilities of diffusion and movement of knowledge, technology, skills, patients, tissues, data, etc., but also their independence of movement.[405] This can allow ethically controversial practices to migrate to more accommodating regulatory environments, just as companies migrate their headquarters to those jurisdictions with the most favourable taxes or regulations.[406] (Thus, in a recent case, a Jordanian couple were treated by a US clinical team with embryos reconstructed in the US, where the embryo transfer took place in Guadalajara, Mexico, with confirmatory genetic testing of biopsied cells being carried out by embryologists from the UK.)

4.31 As practices move between jurisdictions across ethical thresholds, one likely consequence is a form of 'ethical arbitrage' that may have the effect of eroding these differences.[407] This is a matter of concern in relation to technology transfer, particularly across pronounced socio-economic gradients (e.g. between the global north and the global south). In such cases, the introduction of technology can act as a Trojan horse, introducing other forms of dependency on foreign expertise, products and investment and providing a vector for cultural and ethical values, one that potentially contributes further to the diffusion and entrenchment of neoliberalism and market economics. Nation states compete or cooperate with each other ultimately to capture economic benefit and geopolitical power. 'Technonationalism' refers to the hoarding and exploitation of technological advantage by nation states, an outcome that can be supported by a variety of measures including tax incentives, access to markets, patent protections, infrastructure (biotech clusters), exploitability of the research base, amenability of the local language and the adoption of common markets and rules concerning the quality and safety of products placed on those markets.[408]

4.32 National governments may be motivated to adopt such measures in recognition that corporations may care little for the desire of nation states to promote domestic economic growth, seeking instead to exploit their mobility and access to alternative national markets. The diffusion of domestically produced knowledge is a particular kind of problem for states, because it is virtually frictionless. It presents similar difficulties for corporations, however, which could explain why disputes over intellectual property rights (particularly, in the case of genome editing, patent protection) have been prominent.[409] The influence of corporations is, however, only partly responsible for globalisation: nation states, too, have pursued the conditions of free trade by becoming so dependent upon

[405] This dis-integration greatly facilitated the Mexican mitochondrial donation case; on delamination, see: http://www.liminalspaces.ed.ac.uk/files/2018/03/Liminal-Spaces-2018-Workshop-Report-1.pdf.

[406] In legal contexts, where litigants seek to have their claims heard in what they consider more favourable jurisdictions, this practice became known as 'forum shopping', a term that has now gained wider currency.

[407] See also the discussion of slippery slopes in Chapter 2.

[408] See: Edgerton D (2007) The contradictions of techno-nationalism and techno-globalism: a historical perspective *New Global Studies* **1(1)**: 1–32; see also the analysis of British biotechnology research policy in *Emerging biotechnologies*.

[409] The innovation systems of many industrialised countries encourage universities to secure and commercialise intellectual property. (The dispute over the patent claims of University of California, Berkeley and the Broad Institute, MIT and Harvard over the CRISPR-Cas9 platform technology continues at the time of writing.) We return to the question of the contribution of intellectual property to the promotion of the public interest below.

one another that no nation state can reasonably be thought to control its national economy.[410]

4.33 Globalisation has recently provoked a backlash, an overreaction every bit as menacing to cosmopolitan ideals of social justice as neoliberal capitalism.[411] Populism and its reassertion of local cultural values may provide a bulwark against the erosion of ethical borders that has accompanied globalisation. But inasmuch as populism places value on identity and sovereignty, and the biopolitics of populism involves the reassertion of political control over what sort of people may *come into* a jurisdiction, it may also seek to exert political control over what sort of people should come *into being* in a jurisdiction.[412] It is not hard to imagine (given the availability of historical examples from the twentieth century) what the progeny of ethno-nationalism and technonationalism could look like.

International law and governance

4.34 The dominant ethical image of the era of globalisation and, to a large extent, its life support system is a humanism of an individualist sort, which has found a vector in the project to secure a framework of universal human rights, to date the only successfully globalised form of ethics. This project has recently come under attack from majoritarian and identitarian populism.[413] In this section, we consider the relevance to heritable genome editing interventions of international law and institutions and international ethical and political projects.

Specific provisions

4.35 There is no international treaty of general application that directly regulates the human genome or the possibilities for its modification. There are, however, a number of international instruments, inspired by the ambition to secure respect for human rights, which bear on this question in different ways, and at least one important regional treaty that is directly applicable.

4.36 International law provides that once a state has signed a treaty, it is bound to comply with it and has a positive obligation to modify its domestic legislation in order to ensure the fulfilment of its undertakings. In most cases, treaties are accompanied by an infrastructure of oversight or monitoring bodies and some have court systems (e.g. European Court of Human Rights). Additionally, the UK has formally accepted as binding the judgments of the International Court of Justice (ICJ), the principal judicial organ of the United Nations. The ICJ has broad competence to hear all legal disputes concerning questions of international law, the interpretation of treaties, the existence of any fact that

[410] This is equally a problem for economically rich and poor nations; see: Appadurai A (2017) Democracy fatigue, in *The great regression*, H Geiselberger (Editor) (Cambridge: Polity Press), pp.1–12.

[411] Appadurai A (2017) Democracy fatigue, in *The Great Regression*, H Geiselberger (Editor) (Cambridge: Polity Press), pp.1–12.

[412] "Biopolitics concerns the normative exercise of organised power over human bodies and life processes; bioethics concerns normative judgements about the practices and uses of biotechnology and biomedicine. Biomedicine and biotechnologies act, directly or indirectly, on human bodies and are, in many cases, determined by decisions at a public level." It is therefore possible to see the fundamental tangent between biopolitics and bioethics (see: Mills PFR (2016) Brexit and bioethics, *'Nuff said* blog, available at: http://nuffieldbioethics.org/blog/brexit-bioethics).

[413] See, for example: Human Rights Watch (2017) *World report 2017,* available at https://www.hrw.org/sites/default/files/world_report_download/wr2017-web.pdf.

would constitute a breach of an international obligation and to determine the nature or extent of reparation.[414]

Universal Declaration on the Human Genome and Human Rights

4.37 While the Universal Declaration on the Human Genome and Human Rights suggests that practices like 'germ line interventions' *could* be contrary to human dignity, the International Bioethics Committee – the UNESCO body responsible for overseeing the functioning of the Declaration – has not so far, despite a recent re-examination, decided the issue.[415] The 2015 *Report of the IBC on updating its reflection on the human genome and human rights* calls on states and governments (*inter alia*) to agree a moratorium on germ line engineering "at least as long as the safety and efficacy of the procedures are not adequately proven as treatments" and to "Renounce the possibility of acting alone in relation to engineering the human genome and accept to cooperate on establishing a shared, global standard for this purpose."[416]

4.38 The approach taken by the Declaration substantially flows from the value it ascribes to the human genome, the genetic endowment of the species and the importance attached to maintaining the integrity of the human genome. It begins: "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity," although it goes on to acknowledge that the "human genome, which by its nature evolves, is subject to mutations" and that it "contains potentialities that are expressed differently according to each individual's natural and social environment, including the individual's state of health, living conditions, nutrition and education."[417]

4.39 There is a lot going on, conceptually, in this article that links the symbolic, the genealogical and the biological; it employs the concept of 'symbolic heritage' as a way to make the human genome play a fundamental role underpinning both the class unity of all human beings and also the recognition of their inherent dignity and diversity. There is, however, no one thing that corresponds to this that *all* humans have and that no non-humans have. In fact, as many commentators have pointed out, the notion of the 'human genome' is biologically incoherent; the idea that there is a stable pool of genetic variations that can be characterised as 'the human genome' is a fiction (and would preclude all further evolution).[418]

The Oviedo Convention

4.40 Among international human rights instruments, the Council of Europe's *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* (known as the 'Oviedo Convention' and opened for signature on 4 April 1997) is, at the time of writing, the only one that explicitly addresses heritable genetic modification. It has so far been signed by 35 of the 47 member states of the Council of Europe and ratified

[414] See: Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics).
[415] Article 11 of the Declaration mandates that practices contrary to human dignity (it mentions human reproductive cloning explicitly) should not be permitted, and Article 24 mandates the International Bioethics Committee to make recommendations "regarding the identification of practices that could be contrary to human dignity, such as germ-line interventions."
[416] See: http://unesdoc.unesco.org/images/0023/002332/233258E.pdf.
[417] UNESCO (1997) Universal Declaration on the Human Genome and Human Rights, available at: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html; Article 1 and Article 3.
[418] Hitchcock J (2016) Reflections on the law of gene editing *The Biochemist* **38(3)**: 22–5.

by 29, in which states it constitutes binding law. Even those countries, like the UK, that have not signed or ratified the Convention have taken it into account in framing their domestic provisions in many areas of biomedicine such as patient rights, consent and privacy, the protection of biomedical research participants or living donors and in relation to applications of biomedicine such as genetics. Many more states subscribe to similar principles through voluntary and professional codes.

4.41 Article 13 of the Oviedo Convention (entitled 'Interventions on the human genome') provides:

> "*An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.*"

This Article sets out two key principles. The first is that any genome modification (in research or in treatment) should have as its aim a benefit for human health. It does not permit genome modifications that are for other purposes; for example, it does not permit attempts to enhance human characteristics beyond normal functioning or for welfare purposes not related to health.[419] In those states in which the Convention is in force, Article 13 therefore limits, but does not prohibit, genome editing involving human embryos for research purposes.[420] The second key principle is that the aim must not be to introduce changes that can be passed on to future generations; that is, interventions that lead to the birth of children with a modified genome.[421] Whereas the UNESCO Declaration focuses on the integrity of the 'human genome', the Oviedo Convention focuses on the integrity of the inheritance of genetic endowment, in the way in which it forms a web of relations that links all human beings together.

4.42 The stated objective of the Oviedo Convention is "Protecting the dignity and identity of all human beings and guaranteeing everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine." It is important to notice that this objective 'cuts both ways' and, in framing the Convention, the Council of Europe was guided by two main related concerns: first, to ensure protection of individuals against abuse and "misuse of biology and medicine," and second, to promote progress in biology and medicine for the benefit of present and future generations.[422] These concerns have been affirmed at three levels of possible impact: those of individuals, society and the human species (broadly corresponding to the three kinds of considerations discussed in the previous chapter).

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[419] The explanatory report says: 'interventions aimed at modifying genetics characteristics not related to a disease or ailment are prohibited.' Council of Europe (1997) *Explanatory report to the 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*, available at: https://rm.coe.int/16800ccde5; paragraph 90.

[420] The Convention does not take a stand on the acceptability of research on *in vitro* embryos. However, Article 18(1) provides that if national law allows such research, it shall ensure adequate protection of the embryo. The explanatory report says: "If provided for by law, medical research aiming to introduce genetic modifications in [reproductive cells] (spermatozoa or oocytes) which are not for procreation is only permissible if carried out with the approval of the appropriate ethical or regulatory body." The only strict prohibition is laid down in Article 18(2), which prohibits the creation of embryos for research purposes. Article 26 of the Convention provides for the possibility of restriction on the exercise of the rights and protective provisions of the Convention, if prescribed by law and necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedom of others. However, Article 13 is listed among the provisions for which such a restriction is not possible.

[421] It should be observed that, depending on the construction of 'genome' (i.e. whether a person's genome includes their mitochondrial genome) and 'modification' (whether it requires the alteration of a DNA sequence or includes substitutions of subcellular organelles) in this provision, the UK may have already gone beyond the prohibition in Article 13 by legalising and licensing mitochondrial donation.

[422] Oviedo Convention, recitals.

4.43 On its face, Article 13 of the Oviedo Convention appears to prohibit heritable genome editing interventions (although not without some ambiguity).[423] By the same token, according to the preparatory documents, the only clear purpose on which the drafters were resolved was that of prohibiting the use of treatments that carried substantial iatrogenic risk.[424] (It is evident from the preparatory documents that there was significant argument at the time, but no resulting consensus, about whether genome modification should be permitted for the avoidance of serious disease; in the event, the consensus that was achieved was that no technology in prospect at the time – which meant, in effect, recombinant DNA technologies – could be expected to achieve this without unacceptable risk, given the current state of science.[425])

4.44 Both scientific knowledge and (arguably) moral norms have moved on since the Oviedo Convention was drafted. In particular, it is now possible to foresee a situation in which the requisite scientific knowledge might come at last within grasp. In the light of this, and especially the rapid diffusion and development of the CRISPR-Cas9 system, the Council of Europe Committee responsible for overseeing and elaborating the Convention, the Committee on Bioethics (DH-BIO), issued a 'statement on genome editing technologies' in December 2015 (at the same time as the National Academies summit in Washington).[426] The statement recognises the "considerable potential" of genome editing technologies for biomedical research and expresses "strong support for the better understanding of the causes of diseases and for [the development of] future treatment." Significantly, it recognises that, while the principles laid down in the Convention, particularly Article 13, "remain very relevant today" and "could be used as reference for the debate called for at international level on the fundamental questions raised by these technological developments," they are not the last word on the matter. Indeed, the Convention provides for review in the light of scientific developments (initially within five years of its entry into force).[427] This was an important element for some member states when agreeing, in particular, on the provisions of Article 13.[428] It also recognises that public debate is necessary as part of the production of moral knowledge.[429]

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[423] It might be argued that Article 13 of the Oviedo Convention will not apply to all heritable genome editing, at least not to some genome editing carried out for the avoidance of certain genetic conditions. This is because, in such a case, the editing of embryos would be carried out for a preventative reason and, although it would introduce a modification into the genome of potential descendants (i.e. any children of the people those embryos may become), this would not be the *aim* of the procedure (any more than the use of radiotherapy to treat a cancer has the aim of disrupting the DNA of a patient's gametes or of making them infertile. The Article refers to the aims of the procedure precisely in order not to exclude such treatments, as the explanatory report makes clear). While the explanatory report says explicitly that "genetic modifications of spermatozoa or ova [eggs] for fertilisation are not allowed," mention of embryos is oddly absent from this list of prohibited modifications. Here, however, it can be seen that ambiguity about the status of the human embryo causes difficulties in attaching requirements to the correct index case (see discussion about 'consensus' in part 3 of the present chapter below). This is not, however, the obvious construction of the provision, and it is hard to see it as consistent with the purpose that the drafters of the Convention had in mind.

[424] See: Steering Committee on Bioethics (CDBI) (2000) Document CDBI/INF (2000) 1 Prov. entitled "Preparatory Work on the Convention", available at: https://www.coe.int/t/dg3/healthbioethic/texts_and_documents/CDBI-INF(2000)1PrepConv.pdf.

[425] The 'mischief' or moral wrong that the drafters had principally in their sights was not germ line modification *per se* but, in the words of the explanatory report, "modification of the human genome so as to produce individuals or entire groups endowed with particular characteristics and required qualities." It is the mischief also addressed in Article 3 of the EU Charter of Fundamental Rights and that lies behind the UNESCO Declaration; see: Mills PFR (2017) Lame ducks might fly: genome editing, global consensus and geo-ethics *Bioethica Forum* **10(2)**: 68–70.

[426] Committee on Bioethics (2015), document DH-BIO/INF (2015) 13 FINAL entitled "Statement on genome editing technologies", available at: https://rm.coe.int/168049034a.

[427] Article 32.

[428] The monitoring of scientific developments was considered particularly important in the context of the discussion on Article 13 with regard to development in genetics and genomics; see the preparatory documents.

[429] At the time of writing, the DH-BIO has initiatives underway both to review Article 13 and to develop guidance for Member States on public debate under Article 28. The connection between these initiatives is implicit in the 'statement on genome

The EU Charter of Fundamental Rights

4.45 While the UK is not a State Party to the Oviedo Convention and thus not bound by it, it is, for the present, bound by the EU Charter of Fundamental Rights (CFREU), which forms part of the Founding Treaties of the European Union, and the provisions of which are binding on the UK by virtue of its membership in the EU.[430] The Charter does not contain an outright prohibition of heritable genome editing interventions, not least because the EU does not have legislative competence in the area of public health that would allow it to adopt one.[431] Nevertheless, the CFREU contains relevant provisions that were closely based on the Oviedo Convention.

4.46 Article 3 of the Charter (on the right to integrity of the person) prohibits, among other things, "eugenic practices, in particular those aiming at the selection of persons."[432] The extent to which different applications of genome editing discussed in this report are captured by this provision therefore depends on the meaning given to 'eugenic practices'. The Explanations of the Presidium relating to the drafting of Article 3(2) show that the reference to 'eugenic practices' was intended to refer to those practices aiming at the selection of persons in more serious situations, such as those involving "campaigns for sterilisation, forced pregnancy, compulsory ethnic marriage" carried out in Nazi Germany and as part of the ethnic cleansing in Bosnia and Herzegovina.[433] 'Eugenic practices' are, however, not defined, and although the commentary suggests that less serious forms (and not only those perpetrated by states) should also be included, it is doubtful whether the prohibition could apply directly to private decisions and interventions, such as in the case of 'liberal eugenics' described in Chapter 3 above, at least without future domestic legislation to give it that effect.[434]

Box 4.1: The position of the UK after Brexit

On 29 March 2017, the British Prime Minister initiated the process of disengaging the UK from the European Union. When the UK leaves the EU, the extent to which the UK will retain provisions of EU law or be bound by the jurisdiction of its courts, though undecided at the time of writing, may attenuate significantly in the long term. In particular, the UK may further derogate from the Charter of Fundamental Rights established under the Lisbon Treaty in 2007.[435] Britain is nevertheless unlikely to retreat into isolationism and to forswear scientific, economic and geopolitical relationships with

editing technologies' and the fact that both relate to a theme of work on emerging technologies, arising from a conference on this subject in 2015.

[430] This means that the Charter enjoys primacy in domestic law over any conflicting statutes or rules, as well as a direct effect, meaning that it can be relied upon by individuals directly before domestic courts. NB. On signing the Lisbon Treaty, the UK together with Poland appended a Protocol on the Application of the EU Charter; though aimed at limiting the ability to invoke provisions on workers' rights before domestic courts, the Protocol arguably prevents the Court of Justice of the European Union and domestic courts finding inconsistencies between the Charter and UK law.

[431] With the exception of common commercial policy (which extends to the subject matter of biotechnological patent protection under Directive 98/44), the EU has no relevant exclusive competence as regards healthcare under Article 3 of the Treaty on the Functioning of the European Union. However, Article 4 provides that the EU shares competence in public health matters with Member States, if there are common safety concerns, for aspects elaborated in Article 168(4), which include derogations in relation to quality and safety standards for medicinal products, organs, substances, etc., for human use. *Consolidated version of the Treaty on the Functioning of the European Union* (2012), available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT&from=EN.

[432] Cf. Council of Europe (1997) *Explanatory report to the 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*, available at: https://rm.coe.int/16800ccde5.

[433] EU Network of Independent Experts on Fundamental Rights, Commentary of the Charter of Fundamental Rights of the European Union, June 2006, p.40.

[434] See: Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics).

[435] On signing the Lisbon Treaty, the UK together with Poland appended a Protocol on the Application of the EU Charter. Though aimed at limiting the ability to invoke provisions on workers' rights before domestic courts, the Protocol arguably prevents the CJEU and domestic courts finding inconsistencies between the Charter and UK law.

the countries of Europe and elsewhere. The nature of these relationships and what they enable or restrict will depend, to some extent, on moral alignment or the nature of the moral gradient between the UK and the states with which it seeks to interact. Regulatory divergence would be damaging, but economic reality makes this unlikely: UK businesses operating in European markets will still have to follow EU laws after Brexit, so they are unlikely to tolerate additional rules for conducting the same activities at home. To prevent their exodus to the Continent, governments will be strongly incentivised to ensure that UK law mirrors existing and emerging EU rules. The UK could, of course, rejoin the Union at any point, under Article 49 of the Treaty on European Union.

In her letter serving notice of the UK's intention to withdraw under Article 50(2) of the Treaty on European Union, the British Prime Minister affirmed that the UK's decision "was no rejection of the values we share as fellow Europeans." Furthermore, withdrawal from the European Union is legally independent of any relationship with institutions and legal instruments such as the Council of Europe (CoE) and its Conventions. Despite ambivalence within the May Government, the provisions of the CoE's European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR), which are transposed into UK law via the Human Rights Act 1998, form part of domestic law, and the UK remains within the jurisdiction of the Strasbourg Court, independently of its membership of the EU. However, the UK has not signed the CoE instrument most relevant to heritable genome editing interventions, the Convention on Human Rights and Biomedicine ('Oviedo Convention'). Furthermore, although the Conservative Party's manifestos of 2010 and 2015 pledging to replace the 1998 Act and to make the UK Supreme Court the ultimate arbiter of human rights in the UK have been shelved pending Brexit negotiations, its plans may yet take shape.

Other intergovernmental institutions of which the UK is a member, such as the United Nations and its Educational, Scientific and Cultural Organisation (UNESCO) and the Organisation for Economic Co-operation and Development (OECD), also play an active role in ethical debate and establishment of international norms in relation to biomedicine and biotechnology.[436] The UK can be expected to remain active within these as a globally important scientific, technological and political nation.

4.47 It can be seen that these three treaties relevant to heritable genome editing interventions take different approaches to secure similar aims: the UNESCO Declaration focuses on the integrity of the human genome, the Oviedo Convention on the integrity of inheritance and the EU Charter of Fundamental Rights on the mischief of eugenic practices that would select future persons with particular characteristics and exclude others. Beneath the text, however, lies a variety of unresolved considerations, including the nature of concerns that are obscured by the concern about iatrogenic risk. Perhaps as a result of this, some ambiguity still remains, given the operation of novel and imaginable technical approaches and the variety of purposes for which they may be used, about what specifically is prohibited and about where the distinction between what might be permissible and what should be prohibited lies. It is important that the discourse

[436] Organisation for Economic Cooperation and Development (2018) *Gene editing for advanced therapies: governance, policy and society,* available at: https://www.oecd-ilibrary.org/industry-and-services/gene-editing-for-advanced-therapies_8d39d84e-en; UNESCO (2018) *International Bioethics Committee*, available at: http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/international-bioethics-committee/; see also: UNESCO International Bioethics Committee (2015) *Report of the IBC on updating its reflection on the human genome and human rights,* available at: http://unesdoc.unesco.org/images/0023/002332/233258E.pdf.

continues to develop in relation to these instruments, taking account of scientific developments and changing social attitudes.[437]

Other rights and freedoms in international law

4.48 The specific provisions of relevance to heritable genome editing interventions that we have discussed so far are part of a more elaborate governance architecture of entitlements and corresponding obligations. We must consider both how these interventions are specifically provided for and also the way in which they are accommodated within this system. Two sorts of question arise in trying to locate heritable genome editing interventions in relation to this background. They concern, first, the extent to which the objects and practices involved in heritable genome editing interventions fall within the scope of existing provisions and, second, the extent to which people's claims can be fully realised in social and political realities. In addressing these questions, it is helpful to think in terms of the distinction between 'first-generation' civil and political rights that protect fundamental freedoms, where questions of scope are of the first importance, and 'second-generation' social and economic rights that guarantee that a given standard of conduct may be enjoyed by all people equally.[438]

First-generation rights

4.49 Among fundamental civil and political rights, the right to life (the right not to be deprived of life arbitrarily) occurs regularly and early on in a number of international legal instruments. There is, however, disagreement about when this right begins to be engaged and this is usually left unspecified.[439]

4.50 The right to physical integrity is also protected under a number of treaties.[440] Some argue that the prohibition of modifications to the genome (as contained in Article 13 of Oviedo) is an expression of the right to physical integrity extended to encompass genetic integrity.[441] However, this reasoning seems to go significantly beyond the Oviedo reasoning by extending the prohibition to the conduct of research to the protection of future generations.

Non-discrimination

4.51 The discussion of transhumanism (see Chapter 3 above) implies that engineered genetic difference might be a potential source of discrimination. Discrimination could indeed be

[437] The stricture, set out in Article 26(2) of the Oviedo Convention in connection with Article 13 ('Interventions on the human genome'), appears to be a legitimate subject of debate.

[438] The distinction between first- and second- (and third-) generation rights is attributed to the jurist, Karel Vašák, and has been widely adopted in the European discourse on human rights. ('Third-generation' rights are a basket of collective and aspirational rights including many related to securing the enjoyment of the environment.)

[439] The American Convention on Human Rights is exceptional in specifying that the right to life "shall be protected by law and, in general, from the moment of conception." In the UN International Covenant on Civil and Political Rights (ICCPR), however, the vagueness was deliberate and proposals to extend it pre-birth were rejected in the framing of the instrument, with a subsequent amendment to this effect being voted down. (Draft General Comment No. 6 to the ICCPR: Article 6 (Right to Life), Human Rights Committee, para. 7).

[440] An explicit right to physical integrity is provided by Article 5 of the American Convention on Human Rights, Article 4 of the African Charter on Human and People's Rights, Article 3 of the EU Charter of Fundamental Rights, Article 17 of the Convention on the Rights of Persons with Disabilities and Article 1 of the Oviedo Convention. It is also affirmed by in the EU Clinical Trials Regulation and in soft law instruments, such as the Declaration on the Use of Scientific and Technological Progress for the Benefit of Mankind.

[441] According to the Commentary on the CFREU, which is based on Oviedo: "The protection of the embryo against genetic engineering and other unlawful research and the absolute prohibition of any modification in the genome of any descendants illustrates that the protection of the right to personal integrity extends to the unborn children and even to future generations. This represents an important difference to the right to life in Article 2, which in principle is only protected as from birth" (Commentary of the EU Charter, p.39).

'designed in' through the use of genome editing techniques, such as by laying genetic tattoos, rendering subjects sterile or enhancing the reproducibility of edited genes. One potential concern is that of a rogue government determining – we suggest on the frailest of possible grounds – that people born as a result of a heritable genome editing intervention are not technically human, and therefore lack human rights.[442] Such theoretical possibilities invite us to stress test existing laws designed to prevent genetic discrimination. Genetic difference is indeed a protected characteristic for the purposes of the prohibition of discrimination in many international and regional legal instruments.[443] Given that genetic endowment and adventitious damage to the genome play a significant (though rarely determinative) role in so many features (relevantly, to other protected grounds such as health, disability, sex, race, etc.), if genetic endowment is given the status of a protected ground, a difficulty will be to determine where unfair discrimination borders on acceptable grounds for differentiating between people in any given circumstances. (We return to this question below.)

Social rights

4.52 The right to health has been described as a 'second-generation' right; namely, one that is not applicable immediately, but rather is subject to progressive realisation, particularly through anticipated social and technical developments. It is established in numerous international, regional and specialised treaties, arguably making it binding not only under treaty, but also under customary international law.[444] The precise nature of the entitlement that is protected, however, both in terms of what constitutes 'health' for the purposes of this right and the nature of any corresponding positive obligation, is not always clear.[445] The right therefore contains both freedoms and entitlements, the latter being partly dependent on the socio-technical context, including the right to a system of health protection and functioning healthcare facilities, which make the highest attainable level of health available to everyone without discrimination to ensure that the most vulnerable or marginalised sections of the population are not disadvantaged.[446]

[442] The opposite might also apply (i.e. discrimination of those who have not been edited).

[443] Article 11 of the Oviedo Convention prohibits "Any form of discrimination against a person on grounds of his or her genetic heritage" (and the additional Protocol on genetic testing for health purposes adds to this an injunction to take 'appropriate measures' "in order to prevent stigmatisation of persons or groups in relation to genetic characteristics"). The explanatory report makes clear that the concern is the use of predictive genetic testing to reveal non-obvious characteristics that might be a ground of discrimination (and that the argument for the prohibition is made in this light) and that 'genetic heritage' should henceforth be treated as added to the list of protected grounds in Article 14 of the ECHR. Article 21 of the EU Charter does this explicitly by including 'genetic features' among the extensive list of protected grounds set out in its Article 21. Following consultation, the UK government declined to include reference to genetics among the protected grounds set out in the Equality Act 2010.

[444] The right to health can be traced back to Article 25 of the 1948 Universal Declaration of Human Rights and is set out explicitly in: Article 12 of the widely ratified International Covenant on Economic, Social and Cultural Rights to which the UK is a party; Article 55(b) of the UN Charter; the Preamble and Article 1 of the Constitution of the World Health Organization (WHO); Article 35 of the EU Charter; Article 11 of the European Social Charter; Article 24(1) of the Convention on the Rights of the Child; Article 5(e)(iv) of the Convention on the Elimination of All Forms of Racial Discrimination; Article 11(1)(f) of the Convention on the Elimination of All Forms of Discrimination against Women; Article 16 of the African Charter on Human and People's Rights; Article 14 of the Protocol to the African Charter on the Rights of Women in Africa; Article 10 of the Additional Protocol to the American Convention on Human Rights in the Area of Economic, Social and Cultural Rights; and Article 3 of the Oviedo Convention.

[445] 'Health' is defined in the Constitution of the WHO as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"; see also the 1978 Alma-Ata Declaration, International Conference on Primary Health Care, Alma-Ata, USSR, para. 1. It is both a right of individuals and an obligation of states. Scholars such as Saul, Kinley and Mowbray have observed the tension between individual rights and public policy objectives. *The International Covenant on Economic, Social and Cultural Rights: commentary, cases and materials* (2014; Oxford: Oxford University Press), p.978.

[446] CESCR, General Comment No. 14 (2000) The right to the highest attainable standard of health, E/C.12/2000/4, para. 8.

4.53 A specific case of the right to health is the right to maternal, child and reproductive health, which was one of the Millennium Development Goals that, post-2015, have been translated into sustainable development goals.[447] As the right to health may be seen as unfolding over time in accordance with the socio-technical context, it is perhaps not fanciful to imagine that it could, in future, include access to genome editing.[448] There are furthermore specific obligations with regard to medical genetics services, owing to their contribution to furthering the right to health, which could include genome editing techniques.[449] The social nature of this right means that it includes both accessibility and affordability, which, in the case of genome editing, could have public healthcare cost implications for states and entail an obligation to regulate the conduct of private providers to ensure both the quality and accessibility of services.[450]

Freedom of research and the right to the benefits of scientific progress

4.54 The possibility that the right to health might give rise to a positive entitlement to benefit from genome editing may be bolstered by other social rights concerned with the social role of science. In the first place, the freedom of scientific research is defended in a number of treaties as a human right, which creates the expectation of socio-technical change (e.g. the public benefit arising from innovative products and methods) as scientific developments are instantiated in technologies.[451] Freedom of research is in fact part of international customary law, independent of any particular treaty obligations, and is often treated as an outworking of freedom of expression.[452] This means that the freedom to conduct research into genome editing is protected under international human rights law so long as it is not in violation of other human rights. Secondly, there is a widely recognised right to benefit from science and culture or from technological progress.[453]

4.55 Important mechanisms for securing that the freedom of scientific research does not violate the rights of others include requirements for favourable risk or impact assessments, linked to the requirement for due diligence.[454] Related to this are requirements for clinical trials of potential medicinal products as mechanisms to assess risk and controls that exist in many contexts on the conduct of clinical trials. The EU Clinical Trials Regulation provides that "No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity."[455] It is doubtful,

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[447] https://www.un.org/sustainabledevelopment/

[448] "[T]he right of men and women to be informed and have access to safe, affordable and acceptable methods of family planning of their choice, as well as other methods of their choice for regulation of fertility which are not against the law, and the right of access to appropriate health care services that will enable women to go safely through pregnancy and childbirth and provide couples with the best chance of having a healthy infant." Commission on Human Rights, Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, E/CN.4/2004/49, 16 February 2004, para. 18. The final clause, is, of course, delicately ambiguous.

[449] The WHO defines genomics broadly as "the study of genes and their functions, and related techniques." WHO, Resolution WHA57.13 (2004), Genomics and World Health, Preamble, para. 2.

[450] CESCR, General Comment No. 14 (2000) The right to the highest attainable standard of health, E/C.12/2000/4, para. 12.

[451] For example, Article 15 of the Oviedo Convention. The health economics implications of heritable genome editing interventions for health services were discussed briefly in Chapter 1 above.

[452] The EU Charter (Article 13) presents it narrowly as academic freedom of research based on freedom of expression. On customary law, see Article 38(1)(b) of the Statute of the International Court of Justice.

[453] This is found, for example, in Article 15 of the International Covenant on Economic, Social and Cultural Rights, which, as well as protecting publication and freedom of research, provides (at Article 15(4)) for international cooperation. It also occurs in Article 38 of the Charter of the Organisation of American States; Article 14(2) of the Additional Protocol to the American Convention on Human Rights in the Area of Economic, Social and Cultural Rights; Article 32 of the ASEAN Human Rights Declaration; and Article 42 of the Arab Charter on Human Rights. See also: UNESCO Experts' Meeting on The Right to Enjoy the Benefits of Scientific Progress and its Applications (2009) *Venice statement on the right to enjoy the benefits of scientific progress and its applications*, available at: http://unesdoc.unesco.org/images/0018/001855/185558e.pdf.

[454] For example, Article 20 of the Universal Declaration on Bioethics and Human Rights (on 'risk assessment and management').

[455] Regulation 536/2014/EU on Clinical Trials on Medicinal Products for Human Use, and repealing Directive 2001/20/EC, Article 90. Understandably, there is no case law on the Regulation or its predecessor Directive that might help interpret the

however, that *in vitro* genome editing (of embryos, gametes or their precursors) would fall within the definition of a trial, given the indispensable reference to a 'subject' in Article 2, paragraph 2(2) of the EU Clinical Trials Regulation (where a 'clinical trial' is defined).[456] In any case, the clinical trials regime is unsuited to the control of genome editing in a reproductive context, since genome editing can only be carried out as part of a treatment service; there will be no adjustment of the 'dose' and no control groups, the treatment cannot be withdrawn if adverse effects are observed, the consent conditions are more complex (the invasive assisted conception procedure and the use of reproductive materials require different and distinct kinds of consent), and the consent of the parents is not sufficient to exhaust the putative moral duty towards the future person.[457] As we have argued, the introduction of intergenerational genome editing needs to consider a much broader range of norms and consequences. This may be seen as a shortcoming of the US system, where FDA approval of clinical investigations is the sole effective mechanism of oversight.[458]

4.56 A second such mechanism is the denial of intellectual property protections for inventions that could result in violations of human rights or be deemed to impugn human dignity. This has fed down into the EU Directive on the legal protection of biotechnological inventions, which asserts the principle that "the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented."[459] It also asserts that "there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against *ordre public* and morality," and, accordingly, makes provision that "Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality," explicitly indicating that this class of unpatentable inventions is to include "processes for modifying the germ line genetic identity of human beings."[460] Oddly, given the limitations of the EU's competence and the principle of subsidiarity, the force of '*ordre public* and morality' seems rather asymmetrical: states that want to deviate from settled EU morality on the basis of local values face an uphill struggle.[461] Ironically, prohibitions on patenting only *increase* activities that would otherwise have required a

phrase 'germ line genetic identity'. See: Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics).

[456] 'Subject' is defined at paragraph 17 as "an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control." Genome editing might well, however, fall within the definition of a 'clinical study' at paragraph 2(1) of Article 2. An exception arises in connection with the scenario contemplated in paragraph 4.9. In this case, there is a 'subject' – the man whose testes are to be engrafted with edited sperm – as well as a candidate product – the repopulating autologous spermiferous tissue or cells. However, as noted above, it is hard to conceive of such a highly personalised product being marketed, while the exceptions to the Advanced Therapy Medicinal Products (ATMP) Regulation make marketing unnecessary in the first place and a clinical trial for that purpose a rather academic exercise.

[457] Here, there are parallels to the mitochondrial donation process (see http://nuffieldbioethics.org/blog/mitochondrial-replacement-techniques-us-style and also the US National Academies of Sciences report and Cwik B (2017) Designing ethical trials of germline gene editing *New England Journal of Medicine* **377(20)**: 1911–13).

[458] See section on the US at paragraph 4.21ff above.

[459] Recital 16 and Article 5(1), Directive 98/44. The principle is a little incoherent: germ cells are not part of the future body, still less a part of its formation (14 days post-fertilisation, at the earliest, in the human case) or development (unless considered as primordial germ cells of the developing embryo). Although they are part of the body while they form part of a person, this cannot be the case *ex vivo*. In this instance, Article 5(2) and Recital 20 suggest that patentability is not precluded.

[460] Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, Article 6. On the scope of 'human beings' as including embryos to be used in reproductive procedures see Case C-34/10 *Oliver Brüstle v. Greenpeace eV*. [2011] ECR I-09821; Case C-364/13 *International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks* [2014] ECLI:EU:C:2014:2451.

[461] From Case C-165/08 *Commission of the European Communities v Poland*, Judgment of 16 July 2009, in which it was held that Poland could not rely on opposition to genetically modified organism (GMO) release on religious or ethical grounds to derogate from obligations under the GMO Directive. It can be concluded that where a Member State purports to derogate from a EU directive on the basis of public morality, it bears a particularly high burden of proof, one that is not discharged by mere references to the prevailing religious or ethical views of its population or administrative organs.

licence.[462] Investment returns are more readily made from the enabling technologies and from data than from the contentious subject matter, not least because by the time any marketing authorisation has been granted, the patent is likely to have expired.[463]

Dignity and difference

4.57 The nebulous concept of human dignity is often claimed to lie at the root of this legal architecture and, indeed, the requirement to respect human dignity features regularly in jurisprudence and legal argument.[464] Article 1 of the 1948 Universal Declaration of Human Rights (UDHR) affirms that "[a]ll human beings are born free and equal in dignity and rights."[465] Dignity is an important architectural concept that both links human beings to the possession of a human genome and, at the same time, elevates the being of individual humans above the given.[466] Dignity also plays a restraining role. For example, the UNESCO Declaration on Science and the Use of Scientific Knowledge affirms specifically that both "scientific research and the use of scientific knowledge should respect human rights and the dignity of human beings."[467] Notably, the Court of Justice of the European Union has affirmed that human dignity is a general principle of EU law, which can be used to justify restrictions of the obligations imposed by EU law, including the four freedoms (the free movement of goods, services, capital and persons).[468]

4.58 There are two sorts of questions in particular that cause difficulties if the concept of dignity is given anything more than a symbolic, organising function in relation to other rights: first, what do we mean by dignity? And, second, who has dignity? From a legal perspective, the meaning of dignity (or human dignity, as distinct from forms of dignity in which other species may be said to exist) is perhaps most easily understood through its relationship with legal rights.[469] For example, human dignity is the point of tangency between the many instances of the 'respect' due to individuals by others; it casts a protective sphere around individuals, elevating those who have dignity above other forms

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[462] This was the 'harpoon through the foot' effect of the CJEU's decision in *Brüstle v Greenpeace* (Case C-34/10 of 1 October 2011) (on the patentability of inventions ultimately of human embryonic origin). Callaway E (2011) European ban on stem-cell patents has a silver lining *Nature* **478**: 441.

[463] The true value is in the value of data and market exclusivity, as regards marketed cell and gene therapy products.

[464] Dignity has in fact done service for contradictory positions, although the arguments are often less about dignity than about who has dignity (and, in particular, whether embryos have dignity); see: Gottweis H and Prainsack B (2006) Emotion in political discourse: contrasting approaches to stem cell governance in the USA, UK, Israel and Germany *Regenerative Medicine* **1(6)**: 823–9.

[465] Even though not legally binding itself, the majority of the provisions of the UDHR are now seen to reflect custom and therefore have been absorbed into customary international law. The inherent dignity and worth of the human person as the foundation of all human rights are also reaffirmed in the Preamble of the 1945 UN Charter, the Preambles of the 1945 UNESCO Constitution, the 1966 International Covenant on Civil and Political Rights (ICCPR), the 1966 International Covenant on Economic, Social and Cultural Rights (ICESCR), the 1966 International Convention on the Elimination of All Forms of Racial Discrimination (CERD), the 1979 Convention on the Elimination of All Forms of Discrimination against Women (CEDAW), the 1984 Convention against Torture and Other Cruel, Inhuman or Degrading Treatment and Punishment (CAT), the 1989 International Convention on the Rights of the Child (CRC) and the 2006 Convention on the Rights of Persons with Disabilities (CRPD).

[466] Article 1 of the Universal Declaration on the Human Genome and Human Rights asserts that "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity." Article 2 asserts: "(a) Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics. (b) That dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity."

[467] UNESCO Declaration on Science and the Use of Scientific Knowledge (1999), Preamble, para. 19. The UNESCO Declaration on Bioethics and Human Rights asserts that the "ethical issues raised by the rapid advances in science and their technological applications should be examined with due respect to the dignity of the human person…"

[468] Case C-36/02, *Omega Spielhallen und Automatenaufstellungs GmbH v. Oberbürgermeisterin der Bundesstadt Bonn* [2004] ECR I-9609, paras 34–5.

[469] While legal positivists in the Anglo-American tradition might be happy to dispense with dignity altogether, others, particularly in the European humanist tradition, wish to hold on to it as a useful principle and work with it in different ways. Here, we are merely suggesting that a coherent view of what is meant by dignity might be got from an appraisal of its position vis-à-vis first-order rights as these have been put to use, without claiming that it necessarily adds to or explains anything about these rights.

of life, such that each person's interests should have priority over the sole interests of science or of society, upon which only the interests of others with dignity may impinge.[470] On the other hand, this makes the question of who has dignity, if it is posed directly, rather important for the application of these rights.[471] Given its importance, it is rather odd that in one fundamental case – that of the human embryo – an ethical margin of appreciation (the 'space for manoeuvre' granted to national authorities in fulfilling their human rights obligations) has been tolerated amongst states over a long period.[472] It is reasonably clear from decisions by the courts and guidance from relevant institutions that the full protection of the right to life is generally held to begin only with the birth of the child, and similarly, the other rights of the person (including, for example, the right to physical integrity) acquire legal protection only at that time.[473] However, there is an acknowledgment that, in the light of scientific progress and the potential consequences of research into genetic engineering, medically assisted procreation or embryo experimentation, there are some who wish to extend the concept of dignity to provide protections for preimplantation embryos and foetuses in order to provide protection other rights cannot offer.[474] Research that we commissioned on the regulation of genome editing under international law found that in recent decisions, courts have held that:

> "*based on the coinciding approaches of regional human rights courts and domestic bodies, it can be concluded that there is a trend of acknowledging that while embryos and foetuses are not generally recognised as holders of human rights, they are becoming increasingly recognised as having human dignity*."[475]

4.59 We have not taken the approach in this report of developing a concept of respect due to early human life, one to which legal consequences would attach. Instead, we have developed conclusions from socially grounded obligations that arise both in relation to the interests of prospective parents and the anticipation of a future human being who may, in the fullness of time, come to enjoy similar legal protections in their own right.[476] The fact that our approach is socially grounded in this way makes the possibility of a margin of appreciation more explicable (in the sense that it may be stable *in theory* in the long term, rather than being a temporising step on the way to full universal recognition of the concept of dignity), but, as we have observed, it makes it necessary to address

[470] Article 3(2) of the Universal Declaration on Bioethics and Human Rights; Article 2 of the Oviedo Convention.

[471] I.e. if dignity is not either (1) an organising signifier for rights discourse or (2) a concept abstracted from other rights, but a logically foundational concept.

[472] On the 'margin of appreciation', as developed in the Strasbourg jurisprudence, see https://www.coe.int/t/dghl/cooperation/lisbonnetwork/themis/echr/paper2_en.asp.

[473] EU Network of Independent Experts on Fundamental Rights (2006) *Commentary of the Charter of Fundamental Rights of the European Union*, available at: https://sites.uclouvain.be/cridho/documents/Download.Rep/NetworkCommentaryFinal.pdf. p.33, quoting the report of the European Commission of Human Rights in *Brüggemann and Scheuten v. Germany* [1977] DR 10, 100.

[474] See: *Vo v. France*, Judgment, Merits, App No 53924/00, ECHR 2004-VIII, [2004] ECHR 326, 8th July 2004, ECtHR, Grand Chamber, para. 84. One paragraph of the judgment is worth quoting at some length: "At European level, there is no consensus on the nature and status of the embryo and/or foetus, although they are beginning to receive some protection in the light of scientific progress and the potential consequences of research into genetic engineering, medically assisted procreation or embryo experimentation. At best, it may be regarded as common ground between States that the embryo/foetus belongs to the human race. The potentiality of that being and its capacity to become a person – enjoying protection under the civil law, moreover, in many States, such as France, in the context of inheritance and gifts, and also in the United Kingdom – require protection in the name of human dignity, without making it a 'person' with the 'right to life' for the purposes of Article 2. The Oviedo Convention on Human Rights and Biomedicine, indeed, is careful not to give a definition of the term 'everyone', and its explanatory report indicates that, in the absence of a unanimous agreement on the definition, the member States decided to allow domestic law to provide clarification for the purposes of the application of that Convention."

[475] Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics).

[476] We cannot, however, preclude consideration of the establishment of *ex post facto* rights, crystallising at and contingent upon birth, under which an individual acquires legal rights as a person in connection with his or her life before birth.

the practical and political problems of living in an interconnected and interdependent world with persistent ethical differences between jurisdictions.

4.60 Just as the enjoyment of freedoms depends, for individuals, on not infringing the rights of others, states are equally bound by obligations of mutual restraint and the avoidance of 'transboundary harm' for the sake of peaceful coexistence. The obligation to prevent transboundary harm occurs, for example, in the Rio Declaration as a due diligence obligation (i.e. an obligation of conduct rather than an obligation to secure a particular outcome).[477] There will be some argument over the extent to which the erosion of another state's social morality (what we have described as 'ethical arbitrage') might fall into the category of transboundary harm.[478] On the other hand, transnational obligations are also created by the right to health, which requires states to safeguard the right to health in other countries and facilitate cross-border access to healthcare in certain circumstances.[479]

4.61 While states' obligations can extend into other jurisdictions, they can also extent to future generations: a recent development in international law is the elaboration of a principle of 'intergenerational equity', which calls on states to take into account the rights of future generations when undertaking activities that may affect them.[480] The Declaration on the Responsibilities of the Present Generations towards Future Generations contains a reference to the protection of the human genome linked with the preservation of the human species. As we remarked above, this seems somewhat at odds with any prospect of human biological evolution.[481] It seems likely that, if applied to genome editing, the principle of intergenerational equity would require states, as a minimum, to take into account the need to preserve the human species in its diversity for future generations.[482]

Human rights and national sovereignty

4.62 The elaboration of the instruments mentioned (particularly the UNESCO Declaration and the Oviedo Convention) has been described as the 'first steps' in a 'human rights strategy' towards the elaboration of an international biomedical law.[483] This is both a response to the need to govern emerging technologies and a response to the way technologies have been used in the past, emerging, as it did, as "a reassertion of

[477] The 'preventative principle' is the second part of Principle 2 of the 1992 Rio Declaration on Environment and Development.

[478] States' obligations under the preventative principle are codified in Article 3 of the International Law Commission Draft Articles on Prevention of Transboundary Harm from Hazardous Activities, although it is hard to see that 'moral harm' would fall within this definition. On the other hand, states' undermining of the *ordre public* as enshrined in the human rights architecture is likely to be met with profound disapproval – see above in relation to moral succession in the case of the introduction of GMOs in Poland.

[479] See: Commission on Human Rights, Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, E/CN.4/2004/49, 16 February 2004, para. 39.

[480] This occurs, for example, in the preamble to the Oviedo Convention, which establishes "that progress in biology and medicine should be used for the benefit of present and future generations" (para. 1) and also in numerous soft law instruments, such as the UN Declaration on the Rights of Future Generations, which states that "[t]he present generations have the responsibility of ensuring that the needs and interests of present and future generations are fully safeguarded" (1997 UNESCO Declaration on the Responsibilities of the Present Towards Future Generations, Art. 1). Similar provisions can be found in the 1999 UNESCO Declaration on Science and the Use of Scientific Knowledge, para. 39.

[481] The Declaration on the Responsibilities of the Present Generations towards Future Generations provides that "[t]he human genome, in full respect of the dignity of the human person and human rights, must be protected," and that "[s]cientific and technological progress should not in any way impair or compromise the preservation of the human species" (Article 6). Article 16 of the Universal Declaration on Bioethics and Human Rights provides, in similar vein, that states ought to give due regard to "[t]he impact of life sciences on future generations, including on their genetic constitution."

[482] Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics).

[483] See: Andorno R (2002) Biomedicine and international human rights law: in search of a global consensus *Bulletin of the WHO* **80(12)**: 959–63; see also: Ashcroft R (2010) Could human rights supersede bioethics? *Human Rights Law Review* **10(4)**: 639–60.

humanist universalism in the aftermath of the Second World War."[484] It is not surprising that ethical reflection in this context sought out grounding principles that might be shared among people in common (and alighted on dignity as their common root).[485] The embedding of human rights through customary international law (especially through UN actions) and via directly binding legal instruments in many jurisdictions consolidates this move, taking advantage of established systems of law and governance. It has even been proposed that a mature human rights system of concepts, practices and institutions might supersede the disparate and *ad hoc* concepts, practices and interdisciplinary deliberations of bioethics.[486]

4.63 While the proliferation of human rights documents might have been pushing at an open door in the second half of the twentieth century, in the second decade of the twenty-first century, the project has begun to encounter resistance. The undertow of (anti-)political reaction to globalisation, the rise of populist nationalism, the fragmentation of the public sphere through social media and their diverse modes of veracity, anti-intellectualism, the reassertion of national and cultural identities and the rise of new scientific and economic powers not framed by the western philosophical tradition have at best put pressure on the human rights project to regroup in a way that is not seen as complicit with western economic imperialism.[487] The question of consensus has been broached repeatedly in this field. Many commentators and some legal instruments explicitly reference a consensus ('societal consensus' and 'international consensus') that opposes 'human germ line genetic modification'.[488] We have suggested above that this consensus does not exist or, at least, does not have the focus that is attributed to it, and this can only become more evident if the political glue that binds the gamut of human rights objectives together loses adhesion.[489] There are, however, ways other than through the 'top-down' elaboration of legal instruments in which the objectives of human rights may be recuperated.

Soft governance and the public interest

4.64 In this section, we will consider two sites of debate that are relevant to the development of social understandings and the establishment of consensus for genome editing. The first concerns debates among researchers, scholars and professionals; the second, debates in the public sphere, particularly in the media and through various grassroots

[484] The Charter of the United Nations begins: "We, the peoples of the United Nations, determined to save succeeding generations from the scourge of war, which twice in our life-time has brought untold sorrow to mankind…"

[485] In Andorno R (2002) Biomedicine and international human rights law: in search of a global consensus *Bulletin of the WHO* **80(12)**: 959–63, it is claimed that it is "difficult, if not impossible, to provide a justification of human rights without making some reference, at least implicitly, to the idea of human dignity."

[486] See, among others: Faunce TA (2005) Will international human rights subsume medical ethics? Intersections in the UNESCO Universal Bioethics Declaration *Journal of Medical Ethics* **31(3)**: 173–8 and Andorno R (2009) Human dignity and human rights as a common ground for a global bioethics *Journal of Medicine and Philosophy* **34**: 223–40. The claim rests principally on the practical legal and institutional appeal of human rights rather than their intellectual robustness and coherence.

[487] Human rights have, for example, been 'blamed' for retarding industrialisation in developing economies and maintaining them in a state of dependency on western nations. In the context of the rise of populism, particularly anti-science (or anti-expert) varieties, it is apposite therefore to recall Hannah Arendt's dispiriting judgment about the consequences of conflict between national sovereignty and human rights (see chapter on The decline of the nation-state and the end of the rights of man in Arendt H (1951) *The origins of totalitarianism* (New York: Meridian), pp.267–302).

[488] See, for example, the EU Biotechnology Directive: "there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against *ordre public* and morality" (recitals, para. 16). Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0044&from=EN.

[489] See paragraph 4.5647. For some, it is a matter of prudence given the current (or a previously obtaining) state of scientific knowledge; for others, it is not a blanket opposition to genome editing but to the mischief of eugenics.

and public engagement initiatives. The first of these cuts across the national and even regional kinds of formal governance we have discussed so far in this chapter. As we remarked in Chapter 2, the communities of researchers, scholars and professionals often stretch across national jurisdictions. Indeed, to the extent that the development of human knowledge is promoted by the widest exchange of ideas and information and the greatest exposure to critique, such exchanges are the lifeblood of science. While there are national professional and learned societies and membership organisations established for mutual support in specific regulatory contexts, they often have strong international links, participate in frequent international exchanges of information and may even formulate global strategies. Indeed, in terms of their knowledge and interests, and also demographically, culturally and (increasingly) politically, as well as in many other respects, these groups may constitute an international elite in their own right and may have more in common with other elite groups in other nations than with large sections of their national population.[490]

4.65 Publics, on the other hand, tend to communicate intra-nationally as communities with shared interests, subject to locally differentiated markets, political organisations and regulatory forms (although non-governmental organisations (NGOs) may work with similar organisations in other jurisdictions, and international NGOs (INGOs) are established around issues with an international dimension).[491] These interests may transcend other social differences (i.e. the publics may be socially stratified or socially diverse). The Enlightenment notion of the 'public sphere', as distinct from the sphere of political administration, grew in importance in the nineteenth century through political organisation and popular literacy, as political decisions began to have more tangible impacts on greater numbers of citizens. The achievement of a democratic ideal was limited by the dominance of bourgeois interests, the consequence of increasing productivity leading to political complacency and the entrenchment of neoliberal market capitalism.[492] It has a renewed significance, however, in the present social media-saturated era, fragmenting public discourse in a way that can allow reinforcement of beliefs, the admission of alternative standards of truth, propagation of misinformation and perhaps also scorn for evidence, intolerance of criticism and the rejection of expertise in favour of opinion.[493]

[490] The hypothesis is that scientific elites are drawn from similar educational backgrounds and that the relative intensity of their significant communicative activity is conducted more with peers within their disciplines and in related professions, including across jurisdictional boundaries, than with other members of their national polity, and that the former is more meaningful/productive while the latter more functional/transactional. This remains a hypothesis because, in relation to the area of interest, it is not extensively studied. Bibliometrics pioneer Eugene Garfield's work on citation indices to show the propagation of scientific thinking has provided a basis for a few studies to dig deeper into what we might call the 'social interactome' of elite researchers, but his findings are neither conclusive nor generalisable (see, for example: Parker JN, Lortie V, and Allesina S (2010) Characterizing a scientific elite: the social characteristics of the most highly cited scientists in environmental science and ecology *Scientometrics* **85(1)**: 129–43). See also, Nuffield Council on Bioethics (2014) *The findings of a series of engagement activities exploring the culture of scientific research in the UK* (London: NCOB), available at: http://nuffieldbioethics.org/wp-content/uploads/Nuffield_research_culture_full_report_web.pdf.

[491] Many social scientists and public engagement practitioners prefer the plural term 'publics' to the term 'the Public' since this can suggest an inappropriate homogeneity, as if 'public opinion' were something all members of the public share. In many ways, the challenge to democratic processes is to constitute the interest of 'the Public' out of the different and divergent interests of myriad publics, while accepting and respecting non-integrable differences as a part of the political community.

[492] See: Habermas J (1962) *The structural transformation of the public sphere: an inquiry into a category of bourgeois society* (Cambridge, MA: MIT Press, 1991).

[493] In relation to biomedicine, particularly, the question of 'public debate' has recently become a focus of work for the Council of Europe's Bioethics Committee in promoting of the institution's objects of 'human rights, democracy and the rule of law'; see: Council of Europe (2018) *Committee on Bioethics (DH-BIO) terms of reference*, available at: https://rm.coe.int/mandat-18-19-dh-bio-e/168077c5f1.

National academies, learned societies and professional bodies

4.66 An emblematic moment in the history of scientific self-regulation was the Asilomar conference on recombinant DNA technology in 1975, when leading scientists and others with an interest in the technology gathered to carve out a way forward for research that would pacify regulatory concerns about biosafety.[494] Genome editing had its 'Asilomar moment' in early 2015, when the biological researchers who had developed and started working with CRISPR-based techniques began to publish papers about the need to address questions of the governance of genome editing technologies. A significant early paper in this vein was co-authored by Asilomar veterans, David Baltimore and Paul Berg, among others (who included Jennifer Doudna and George Church, two of the inventors of the CRISPR-Cas9 technique), seeking a "prudent path forward for genomic engineering and germline gene modification."[495] This had two salient elements (a self-denying ordinance to the effect that there should be no move to implement heritable genome editing interventions) coupled with an appeal for broader-based debate orientated towards an implicit objective (to permit the continuation of research without interference).[496] Since then, the franchised 'open discussion' has been taken up and broadened out by a number of other bodies, organisations and groups.[497]

4.67 A group of the most significant UK medical research funders, academies and organisations, marshalled by The Wellcome Trust, published a statement on genome editing in September 2015.[498] Their position was not to support the application of heritable genome editing interventions, but to leave the possibility open as research and policy develop. This was intended to provide a bulwark against anticipated calls for a moratorium on genome editing research for human applications. It was followed by interventions from a number of international scientist-led groups. The Hinxton Group (named after the location of the initial meeting in Hinxton, Cambridgeshire) arose as an international interdisciplinary convocation to explore the ethical and policy challenges of transnational scientific collaboration in human embryo and stem cell research. The Group published a consensus statement in September 2015 calling, among other things, for a roadmap for research to establish the safety of genome editing for use in humans.[499] International meetings of a similar profile and with similar effect were organised, for example, by the Federation of European Academies of Medicine (FEAM). At the time of writing, policy positions have been promulgated by FEAM, the International Society for Stem Cell Research (ISSCR), jointly by the European Society for Human Reproduction and Embryology and the European Society for Human Genetics (ESHRE-ESHG), the

[494] For background and a brief discussion, see: Nuffield Council on Bioethics (2016) *Genome editing: an ethical review* (London: NCOB), para 3.6 ff.

[495] Baltimore D, Berg P, Botchan M, *et al*. (2015) A prudent path forward for genomic engineering and germline gene modification, *Science* **348(6230)**: 36–8.

[496] This, from within a 'procurial' frame, could be interpreted as an opening into a kind of 'ethical choreography' as elaborated influentially in Thompson C (2013) *Good science, the ethical choreography of stem cell research* (Cambridge, MA: MIT Press).

[497] The phrase 'open discussion' is the one used in the Baltimore *et al*. paper, although the vision for this discussion is of one that is interdisciplinary but elite. The scientific establishment's move to include a broader range of social actors begins (arguably) with the National Academies' summit, albeit here only by including 'members of the general public' in an organised international forum, and with the Council of Europe Bioethics Committee statement, which invokes Article 28 of the Convention on the promotion of public debate and the requirement for public consultation.

[498] Initial Joint Statement on Gene Editing in Human Cells (available at: https://wellcome.ac.uk/what-we-do/our-work/our-policy-work-gene-editing) signed by AMS, AMRC, CRUK, BBSRC, MRC, PPET, Sanger and Wellcome.

[499] Statement on Genome Editing Technologies and Human Germline Genetic Modification (available at: http://www.hinxtongroup.org/Hinxton2015_Statement.pdf). Nuffield Council member, Andy Greenfield, attended the meeting, but participated only as an observer.

European Academies' Science Advisory Council (EASAC) and the American Society of Human Genetics (ASHG), among others.[500]

4.68 As well as these international scientific groups, a number of national learned societies and research institutes have also set down their position on heritable genome editing, filling out the spectrum of positions from endorsing research alone (for the time being) to plotting a pathway to eventual translation into the clinic, from raising points for consideration to setting out firm recommendations. These include the German academy of sciences, the Leopoldina, the French medical research institute, Inserm, and COGEM (the Netherlands).[501] These have been accompanied by opinions, statements and discussion papers from national ethics councils, including the Deutsche Ethikrat, the Swedish, and Danish Councils and the European Group on Ethics in Science and New Technologies (EGE).[502]

4.69 One of the most sustained inquiries carried out to date was by a study group convened by the US National Academies of Sciences and of Medicine, which produced a consensus report in February 2017.[503] The report finds that arrangements for basic research and somatic genome editing treatments are broadly appropriate in the US, although it has an eye to governance in other countries as well. It also foresees the possibility of 'germ line' applications in clinical trials for 'compelling reasons', once risk–benefit questions have been more carefully addressed. It foresees the use of somatic genome editing for 'enhancement' purposes in the future, but recognises that the liminal questions about health and enhancement are difficult to answer, as well as evaluative questions about the balance of risk and benefit. While the report finds the social consequences of genome editing to be an important consideration, it expects the initial uses of heritable genome editing interventions to be rare and exceptional. Like many other reports, it affirms the need for broad public engagement, although a particular focus of this is as input to permission decisions. Interestingly, the report identifies a number of principles that it argues should govern the introduction of genome editing in both somatic and reproductive treatments, which it presents as a possible basis for a project to reach international consensus. Though the principles themselves are so broad as to be used

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[500] See: FEAM (2017) The application of genome editing in humans, available at: http://feam.cmail20.com/t/ViewEmail/j/3EE4637CE79950882540EF23F30FEDED/1011218CCFF091C02438807772DD75D1 ; ISSCR (2016) Guidelines for stem cell science and clinical translation, available at: www.isscr.org/guidelines2016; de Wert G, Pennings G, Clarke A, *et al*. (2018) Human germline gene editing: recommendations of ESHG and ESHRE *European Journal of Human Genetics* **26(4)**: 445–9; EASAC (2017) *Genome editing: scientific opportunities, public interests, and policy options in the EU*, available at: https://easac.eu/publications/details/genome-editing-scientific-opportunities-public-interests-and-policy-options-in-the-eu/; Ormond KE Mortlock DP, Scholes DT, *et al*. (2017) Human germline genome editing *American Journal of Human Genetics* **101**: 167–76.

[501] Leopoldina, ACATECH and UNION (2015) The opportunities and limits of genome editing, available at: http://www.leopoldina.org/uploads/tx_leopublication/2015_3Akad_Stellungnahme_Genome_Editing.pdf; Inserm (2016) *Fostering responsible research with CRISPR-Cas9: Inserm Ethics Committee Workshop, 16 March 2016*, available at: https://www.inserm.fr/sites/default/files/media/entity_documents/Inserm_Programme_CR_ComiteEthique_Atelier_201603_0.pdf; COGEM (2017) Editing human DNA: moral and social implications of germline genetic modification, available at: https://www.cogem.net/index.cfm/en/publications/publication/editing-human-dna-moral-and-social-implications-of-germline-genetic-modification?order=relevance&q=genome+editing&category=&from=30-09-1998&to=29-06-2018&sc=fullcontent.

[502] Deutcher Ethikrat (German Ethics Council) (2017) *Germline intervention in the human embryo: German Ethics Council calls for global political debate and international regulation*, available at: https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/englisch/recommendation-germline-intervention-in-the-human-embryo.pdf; SMER (The Swedish National Council on Medical Ethics) (2015) *SMER comments: the technique CRISPR-Cas9 and possibilities to edit the human genome*, available at: http://www.smer.se/news/smer-comments-the-technique-crispr-cas9-and-possibilities-to-edit-the-human-genome/; Det Etiske Råd (Danish Council of Ethics) (2016) *Statement from the Danish Council on Ethics on genetic modification of future humans In response to advances in the CRISPR technology,* available at: http://www.etiskraad.dk/~/media/Etisk-Raad/en/Publications/Statement-on-genetic-modification-of-future-humans-2016.pdf?la=da. Many of the interventions, particularly the earlier ones, which start with the scientific developments and tend to mark out questions rather than deliver recommendations, range across a variety of fields of application beyond heritable human genome editing (as did our own 2016 report, *Genome editing: an ethical review*).

[503] National Academies of Sciences, Engineering, and Medicine (2017) *Human genome editing: science, ethics, and governance*, available at: https://doi.org/10.17226/24623.

to support contradictory conclusions, they nevertheless offer a potential focus for argument and discussion about specific applications.

4.70 Perhaps of most interesting among the various publicly salient interventions relating to heritable genome editing are a number of *ad hoc* initiatives that have strained towards interdisciplinarity. Most conspicuous among these to date was the international summit held in Washington, DC, in December 2015 and hosted jointly by US National Academies of Sciences, Engineering and Medicine, the Chinese Academy of Sciences and the UK's Royal Society. The summit organising committee produced a statement saying it would be 'irresponsible' to undertake human germ line editing at present, but called for continuing discussion and review in the light of scientific evidence.[504] Two conclusions in particular are noteworthy. The first is the opinion that it would be 'irresponsible' to proceed with clinical use of heritable genome editing in the absence of a 'broad societal consensus' about the appropriateness of the proposed application. The second is the practical proposal for an international forum, with the ambition to harmonise regulation, which would include a cross-section of stakeholders including 'members of the general public'.[505] While no one has picked up the baton to establish a forum with quite the scope envisaged by the Washington summit organising committee, a number of other initiatives have the ambition or the potential to give effect to it. One such is an initiative that grew out of work undertaken by the French medical research institute, Inserm, which has resulted in the formation of an International Association for Responsible Research and Innovation in Genome Editing (ARRIGE) and grown into a multidisciplinary grouping of individuals from more than 35 countries.[506]

4.71 In their first sallies into the public sphere, researchers and other participants were quick to defend the protected space for research and reject any suggestion that this would segue automatically into clinical practice. Their initial interventions can be seen as having a dual purpose: to achieve a *segregation* of basic from applied research (and thereby to protect the former) and to impose *linearity* on the process (to mark out a managed pathway of orderly and controlled development). This linearity allows the formation of a narrative in terms of teleology (an explanation in terms of aims) that stands partly as a rationale for research. It also seeds expectations, beginning the process of acculturation to projected future states of affairs and linking the development of particular technologies to identified societal challenges.[507]

4.72 Several features of genome editing, however, fit poorly with this narrative. First, the distinction between 'basic' and 'applied' research (in the case of embryo editing) may be

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[504] See: Organizing Committee for the International Summit on Human Gene Editing (2015) On human gene editing: international summit statement, available at: http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a. Andy Greenfield attended on behalf of the earlier Nuffield Council working group and Charis Thompson gave a presentation in one of the sessions. The Washington summit was held contemporaneously with the DH-BIO meeting in Strasbourg, which produced the statement discussed above.

[505] "We therefore call upon the national academies that co-hosted the summit – the US National Academy of Sciences and US National Academy of Medicine; the Royal Society; and the Chinese Academy of Sciences – to take the lead in creating an ongoing international forum to discuss potential clinical uses of gene editing; help inform decisions by national policymakers and others; formulate recommendations and guidelines; and promote coordination among nations. The forum should be inclusive among nations and engage a wide range of perspectives and expertise – including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public."

[506] www.arrige.org

[507] On the need for teleology, see: 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. This is not to suggest that there is anything pernicious about this, only to reveal its workings in order to identify further possibilities of agency.

a 'distinction without a difference', one that depends not on the practice itself, but on circumstances (in other words, exactly the same intervention may be used to research and to achieve genetic modification, the only difference being that in the former case, the embryo is not transferred).[508] Second, the relative accessibility of the CRISPR-Cas9 system means that it is available to users who are not part of the elite scientific community and are not socialised or engaged in the public discourse. This is a conspicuously different state of affairs from that of recombinant DNA in the 1970s and includes competitors seeking 'global firsts', mavericks, rogue states and even, potentially, DIY biology enthusiasts. Third, the global portability of knowledge, skills, technologies, tissues and patients mean that these can flow freely between states and communities, making ethical gradients difficult to maintain and providing opportunities for what we described above as 'moral arbitrage'.[509] Whereas science imagines linearity and orderly innovation, technoscience involves diversions, function creeps and discontinuities. All of this suggests that heritable genome editing does not belong to, nor is it within the control of, a notional 'Republic of Science'.[510] It is already an issue for broader society, and the determinants of future research and innovation now necessarily involve publics, policy makers, commercial actors and others (e.g. national security advisors).

Public debate

4.73 Heritable genome editing technology connects readily with (and forges new connections between) a number of issues that have historically attracted high levels of public interest, such as genetically modified organisms (which engage views about promethean manipulation of 'Nature'), assisted conception (the relief of infertility), cloning (asexual reproduction, 'three-parent babies'), biomedicine (revolutionary, life-saving treatments), reproductive genetics ('designer babies') and the treatment of embryos (religious and philosophical views about the status of early human life). These earlier debates constitute a background of cultural memory, informal knowledge and expertise that could easily be mobilised in relation to heritable genome editing interventions, although this has yet to find the sustained focus that it might get, for example, from a proposal to change the law or from news of a pioneering treatment (a new 'test tube baby'). These issues are also fomented in popular culture through a large number and wide variety of films, novels, plays and other cultural forms, which dramatise socio-technical imaginaries, policy decisions and moral judgments. Deliberate initiatives have also been taken to engage a wider range of people, such as Progress Educational Trust conferences and the 2017 and 2018 'Festivals of Genomics', which included a number of sessions on CRISPR and genomics, including presentations and panel discussions to communicate the science to a general audience and provide opportunities to debate the issues it raises.[511] Nevertheless, while there has been a considerable amount of interest

[508] This is similar to the largely linguistic distinction between 'therapeutic' and 'reproductive' cloning that did service in international diplomacy around the turn of the century.

[509] An example of this might be the 'Mexican mitochondrial donation case'; see paragraph 4.17.

[510] In a famous essay, 'The republic of science', the polymath, Michael Polanyi, who was concerned with the relation between scientific freedom and the public good, wrote: "The more widely the republic of science extends over the globe, the more numerous become its members in each country and the greater the material resources at its command, the more clearly emerges the need for a strong and effective scientific authority to reign over this republic." Polanyi M (1962) The republic of science: its political and economic theory *Minerva* **I(1)**: 54–73.

[511] Progress Educational Trust (2016) *Rethinking the ethics of embryo research: genome editing, 14 days and beyond*, available at: https://www.progress.org.uk/conference2016; Progress Educational Trust (2017) *Crossing frontiers: moving the boundaries of human reproduction*, available at: https://www.progress.org.uk/conference2017. The 2017 Festival of Genomics (London, 31 January–1 February) included a number of sessions on CRISPR and genomics, including a panel discussion on 'Editing the human embryo, an update and discussion', chaired by working party member, Tony Perry. ExCel London (2018) *Festival of genomics London*, available at: https://www.excel.london/whats-on/festival-of-genomics-london. Tony also spoke on 'Genome editing and its implications' at the Bath Royal Literary and Scientific Institution on 23 February

in genome editing in the popular science and business press, on websites and in the blogosphere, it has only sporadically crossed into the mainstream media as a news or 'human interest' story.[512]

4.74 A number of specific initiatives have undertaken to engage non-specialists in order to establish where the general balance of opinion lies or to research communication or opinion formation in this area. An example of the first is a series of questions on three potential human 'enhancement' technologies put to a nationally representative panel of 4,726 randomly selected US adults carried out in 2016 by the Pew Research Center.[513] An example of the latter is a survey of a diverse sample of 2,493 Americans carried out by researchers from the University of Pennsylvania to examine the influence of different framings of heritable genome editing.[514] There have also been initiatives to gather the views of more specific stakeholder groups, such as a 2016 report *Genome editing technologies: the patient perspective* produced by Genetic Alliance UK (GAUK), an umbrella group of over 180 patient organisations representing patients and families affected by genetic conditions.[515] Our own online questionnaire, which drew 320 responses, albeit from a self-selecting sample, provided a substantial volume of detailed, qualitative information on views that respondents had relating to heritable genome editing and their reasons for holding those views.[516] Our *Call for evidence* also gathered responses from a number of stakeholder groups with distinct and principled positions.[517] These examples are only a small selection from a growing number of initiatives, however.

4.75 Qualitative research involving more sustained dialogue with sections of the public has been also been carried out; for example, research into communicating with publics about genome editing, carried out by the Progress Educational Trust and GAUK[518] and research exploring public views, on behalf of the Royal Society.[519] These 'extractive' exercises are all valuable in developing understanding of public attitudes and reasons, and potentially informative for decision makers, although none is directly connected as yet with the sites of agenda setting for research or political decision making. If, as we said above, the prospect of heritable genome editing interventions engages questions of social norms and potentially also affects these norms – that is, it both reflects and affects

2017. The 2018 Festival of Genomics (London, 30–31 January) included a presentation on genome editing by Tony Perry and a panel discussion chaired by Council member, Andy Greenfield, on which Nuffield Council staff member, Peter Mills, was a panellist.

[512] There has been a steady flow of stories about technological developments, the personalities involved, their battles over intellectual property rights and the medical and commercial prospects of genome editing in magazines such as *New Scientist*, *Wired* and *The Economist*. An example of genome editing as a 'human interest' story was the BBC1 programme *The big questions* (28 May 2017) on the subject 'Is interfering with genes ethical?'; working party member, Jackie Leach Scully, was a participant (along with ex-Council Chair, Jonathan Montgomery).

[513] The other technologies were implanted brain chips for improved concentration and information processing and synthetic blood transfusion for greater speed, strength and stamina (see: http://www.pewinternet.org/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/)

[514] Weisberg SM, Badgio D, and Chatterjee A (2017) A CRISPR new world: attitudes in the public toward innovations in human genetic modification *Frontiers in Public Health* **5**: 117. The prospective technology was presented in the 'frames' of 'editing', 'engineering', 'hacking', 'modification' and 'surgery'.

[515] The report is available at: https://www.geneticalliance.org.uk/media/2623/nerri_finalreport15112016.pdf; it found support among GAUK members for exploring both the therapeutic and reproductive possibilities of genome editing for those affected by genetic diseases.

[516] The detailed findings (including the raw data collected in response to the questions) were discussed by the working party at its meeting in December 2017 and informed the development of the present report (see Appendix 1).

[517] See Appendix A.

[518] Progress Educational Trust, Genetic Alliance UK (2017) *Basic understanding of genome editing: the report* (available at: https://www.progress.org.uk/genomeediting); see also: Starr S (2018) How to talk about genome editing *British Medical Bulletin* **126(1)**: 5–12.

[519] van Mil A, Hopkins H, and Kinsella S (2017) *Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society*, available at: https://royalsociety.org/~/media/policy/projects/gene-tech/genetic-technologies-public-dialogue-hvm-full-report.pdf.

the 'moral fabric of society' that is partly reflected in norms of law and governance – then a more sustained consideration of how the public interest is produced becomes important.[520]

4.76 While genome editing as a technical approach to heritable genetic modification is a relatively new phenomenon for public interest, in the UK (as we have described above), it is already provided for by existing legal and other arrangements. As we have also suggested, however, the potential of prospective genome editing technologies is distinct from that of previous approaches; furthermore, both social values and understandings are subject to evolution: the future (as they say) is not what it used to be.[521] While the public interest is, as we suggested above, likely to draw on existing cultural knowledge and established values, in the absence of more specific elucidation, it cannot be inferred with complete reliability.

4.77 How the public interest is produced and connected to the governance of technologies is itself a matter of significant public interest. Consistently with the conclusions of other Nuffield reports and for reasons that apply across the gamut of emerging biomedical technologies and biotechnologies, there are good reasons to advocate deliberative modes of engagement rather than purely competitive or economic ones (such as casting lots) in relation to heritable genome editing technologies. These have the dual function of both constituting the moral community (the 'public') though the engagement among citizens under government and producing a representation of the 'public interest' (rather than simply the result of competition between the interests of different publics). We make recommendations relating to the public engagement with the governance of heritable genome editing technologies, among other aspects of governance, in the next section.

Governing heritable genome editing technologies

4.78 In this final section of the chapter, we make recommendations, in the light of our foregoing discussion, about what we consider to be desirable amendments to existing governance or areas that we believe require further examination. We also make recommendations about constructive initiatives that might contribute to ethical governance in the most general sense.

Amending the rules

Law

4.79 First of all, there should be no rush to amend existing legal rules, at least in the UK. As we have observed above, UK legislation (with the possible exception we have noted in paragraph 4.9) adequately covers the techniques of intergenerational genome editing that we have been discussing in this report. Our reason for prioritising this area of inquiry was not that the technology was ready for human use, although some techniques may be closer than others and closer than many people believe. Our reason was that there will be a significant lead time if there are to be any changes to policy and legislation. Not

[520] We say the public interest is 'produced' rather than 'discovered' or 'identified' because there is possibly not an *a priori* public interest in heritable genome editing that exists independently of the question, any more that there is a 'public' independently of an issue that brings it into being. What we are interested in here is therefore political processes of the production of the public interest rather than the elicitation of a pre-existing interest.

[521] This difference was brought out strongly by the contrasting approaches of researchers (who wanted to consider possible pathways to reimagined futures) and policy makers (who were content that every plausible future was already provided for) at a workshop held on 17 March 2016. The event brought together researchers and research funders, policy makers, and dialogue specialists. A report of the workshop, *Public dialogue on genome editing: Why? When? Who?* is available at: http://nuffieldbioethics.org/wp-content/uploads/Public-Dialogue-on-Genome-Editing-workshop-report.pdf.

hurrying to change the legal rules does not mean that we should not address ourselves to this prospect, but rather that we should begin to do so in a way that is most likely to allow the opportunity for full and inclusive debate. Therefore, **we recommend that, before any move is made to amend UK legislation in order to permit heritable genome editing interventions, there should be sufficient opportunity for a broad and inclusive societal debate**. Furthermore, **we recommend that broad and inclusive societal debate about heritable genome editing interventions should be encouraged and supported without delay**.

4.80 To delay the debate until technologies are at hand would be to allow a situation to come about in which there probably would be pressure to legislate in a hurry, almost inevitably in the context of demands from prospective patients to be permitted to use the technologies. The reason for engaging with the question now is not, however, to avoid it being clouded by personal and passionate representations. What we mean by 'broad' in this context is that the debate should not focus upon the use of a specific reproductive technology. Rather, such debate should be conducted in terms of the framing, evaluation and prioritisation of societal challenges and of the diverse ways of addressing them without that discussion being narrowed around a presumptive technological 'solution'. This is one reason why we do not think that such a debate should be led by a sector regulator. In our 2016 report of a workshop on public dialogue we concluded that researchers and funders involved in genome editing have a responsibility to promote such debate as part of responsible research and innovation (RRI) practice.[522] But the scope needs to be much broader, which would benefit from additional institutional support. We discuss this notion of broad and inclusive societal debate further below and make additional recommendations about how this might be facilitated.

4.81 If heritable genome editing interventions were ever to become permissible in the UK, it would require revision of the existing framework legislation: the Human Fertilisation and Embryology Act 1990.[523] Such a revision would likely be similar in scope to the 2008 revision of the Act under which powers were inserted to make Regulations (in effect) to permit mitochondrial donation. Changing primary law is potentially of much greater consequence than exercising the power to make Regulations (notwithstanding that the 2015 Regulations engaged many sections of the public and were debated in both houses of the UK Parliament) because it allows unrestricted opportunity to amend or repeal the provisions of the Act or to insert new provisions that relate to matters within the scope of the legislation.[524] In view of the fact that many other contentious issues are likely to come to the fore in a general revision of legislation (such as perennial debates about the controls on termination of pregnancy included in the Act) and because these may detract from or obscure (although they may also help to triangulate) the question of heritable genome editing, we think that the broad public debate on heritable genome editing

[522] See: Nuffield Council on Bioethics and Sciencewise (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), in which we characterised RRI in the following terms: "RRI broadly encourages researchers and innovators to consider fully the implications of their research and consider how to engage with others in reflecting on the wider societal interest in science as a source of society's response to its material conditions. It emphasises democratic determination of how science is orientated towards the achievement of desirable futures, the recognition of uncertainties in the way in which scientific knowledge plays out in the wider world, and the need for built-in responsiveness to these uncertainties on the part of infrastructures and institutions" (p.14).

[523] As discussed above, there are two exceptions to this: it might be permitted for the sole purpose of avoiding mitochondrial diseases through Regulations, and the modification of spermatogonia is arguably not within the scope of that Act.

[524] Given that the Act provides for a multitude of contentious matters (including and especially that votes on this are conventionally not 'whipped' by political parties), opening up the legislation in this way necessarily entails some risk or opportunity to the interests that are engaged. The scope of the legislation is effectively given in its long title.

interventions should be encouraged independently of any policy process to review the Act as a whole.

4.82 As we observed above, the legal situation of mitochondrial diseases is exceptional in relation to other genetic conditions in a way that seems somewhat contingent on research that was in train at the time of the passage of the 2008 Act. This difference suggests consideration should be given to differences in the ways that different conditions and different techniques are provided for, anticipating the possibility that a technique with comparable clinical feasibility to the (now licensed) techniques of mitochondrial donation should become available. In 2015, it would not have made sense to exercise the powers in the Act to the fullest extent possible for the sufficient reason that no demonstrably reliable technique was then available (or is available now) to avoid mitochondrial DNA disorders that are associated with nuclear DNA rather than mitochondrial DNA. It is clear from parliamentary debates around this time, however, that another issue in view (and which Parliament decided, at the time, to foreclose) was that of human DNA modification.[525] In other words, the debate became caught up on distinguishing (and attaching significance to those distinctions) between cell reconstruction and altering the sequence of bases in a nuclear DNA molecule, between 'germ line modification' and 'genetic modification'.

4.83 From the point of view of clinical feasibility, it cannot be said at present whether the techniques of genome editing will prove to be any more or less safe, or any more or less effective in securing their aims, than maternal spindle or pronuclear transfer techniques (the cell reconstruction procedures developed for mitochondrial donation). These are technical questions and require further and continuing research.[526] It is plain from our conclusions in Chapter 3 above, however, that we do not regard intentionally modifying the germ line (the cells that contain the genetic endowment that is passed on between generations), or, more specifically, genetic modification of nuclear DNA within the germ line, as morally impermissible in and of themselves.[527] In view of this, **we recommend that research to establish the clinical safety and feasibility of genome editing should be supported in the public interest in order to inform the development of evidence-based standards for clinical use**. Furthermore, in view of our discussion of the concept of welfare in Chapter 3 and the relevance to this of other factors in addition to physical well-being, **we recommend that social research that would help to understand the welfare implications for people born following heritable genome editing interventions (e.g. involving people born following preimplantation genetic testing) should also be supported in the public interest**.

4.84 In addition to issues that might be addressed by such research, the comparison with mitochondrial donation draws attention to the purposes for which the procedures are carried out (mitochondrial diseases versus other genetic diseases, genetic diseases versus other genetically conditioned characteristics, such as predisposition to complex disease, susceptibilities to environmental conditions, disease resistance, etc.). Our conclusions in Chapter 3 that led us to propose the two cardinal principles (the 'welfare of the future person' principle and the 'social justice and solidarity' principle) suggest that morally permissible or desirable reasons for using genome editing cannot simply be

[525] See, for example, *Official Report* ('Hansard') HL Deb 24 February 2015, Col .1569 ff.

[526] In one respect, at least, genome editing may be less problematic than mitochondrial donation since it is more precise and does not require the third-party donation of genetic material, with the issues of donor protection and compatibility that this entails (not to mention residual problems of carry-over of disease-variant mitochondria).

[527] Mitochondrial donation can be said to be 'germ line modification' but not 'genetic modification' because the germ cells involved undergo alteration and the altered versions can be passed down through the maternal line to subsequent generations, although neither the sequence of DNA bases of any of the donated mitochondria nor that of the nucleus is altered. On related issues, see: Haimes E and Taylor K (2017) Sharpening the cutting edge: additional considerations for the UK debates on embryonic interventions for mitochondrial diseases *Life Sciences, Society and Policy* **13**: 1–25.

drawn along problematic demarcations between disease or non-disease characteristics. What is required is a legitimate and effective regulatory procedure combined with continual reflection on marginal cases, not only in terms of whether they are permissible according to some categorical principle but, importantly, also in terms of the human and societal implications of their implementation in assisted reproduction services.

4.85 We have been concerned in this report not merely to consider the narrow impact of heritable genome editing interventions on individuals and families, but also to think about what the implications of using genome editing might be more generally. For most potential indications (barring those that are extremely rare or unique to a particular family), there are potentially a number – possibly a large number – of prospective parents who might wish to access the treatment and who would be good candidates to do so. We need to consider the implications of patterns of access and provision more generally. One measure that can help to give effect to our 'social justice and solidarity' condition is therefore a prior impact assessment that strives earnestly to anticipate and envision (and not merely passively to detect) potential secondary or unintended consequences; therefore, **we recommend that heritable genome editing interventions should be permitted only provided that the impact on those whose vulnerability to adverse effects (including stigmatisation and discrimination) might thereby be increased has been assessed and mitigated (and, in any case, not without open and inclusive consultation with people in those positions)**.

4.86 As well as the effects on individuals directly involved, we have been concerned also in this report with the social effects of genome editing, which are less obvious but potentially far-reaching and significant. Therefore, complementary to the prospective impact assessment we have recommended above, **we recommend that heritable genome editing interventions should only be permitted provided that arrangements are in place to monitor the effects on those whose interests may be collaterally affected and on society more generally, and provided that legitimate and effective mechanisms are in place to redress those effects and to revise relevant policy; this should include a clear regulatory measure to trigger a moratorium and a sunset provision, requiring review and an affirmative resolution to permit the practice to continue**. In the final part of this chapter, we propose the kind of institutional arrangement that we believe would support this and other recommendations we make concerning how heritable genome editing interventions affect and engage wider society.

4.87 Finally, we have noticed that the current provisions that require the licensing of assisted conception procedures may not wholly extend to cover sperm derived from modified and re-implanted spermatogonia (see Chapter 2 and above). (Alternatively, if they *do* govern such sperm, they might have the implication of making it unlawful for a man in such a situation to have sexual intercourse – which might, in turn, be incompatible with his human rights.) If this situation is considered anomalous and undesirable, a remedy would be to make regulations under section 1(6) of the 1990 Act (as amended).[528] This section allows the Secretary of State, for the purposes of the Act, to bring within the definition of sperm, eggs or embryos things that are not presently so defined, and thereby to bring them under the control of the Act. This might appear to be unnecessary as the procedure is at present somewhat far-fetched and the risk of someone undertaking it simply to

[528] "If it appears to the Secretary of State necessary or desirable to do so in the light of developments in science or medicine, regulations may provide that in this Act (except in section 4A [which provides for genetic material not of human origin]) 'embryo', 'eggs', 'sperm' or 'gametes' includes things specified in the regulations which would not otherwise fall within the definition." HFE Act 1990, s.1(6).

circumvent HFEA regulation (which they might otherwise do by travelling to a different jurisdiction) seems low. Nevertheless, **we recommend that, without awaiting the opportunity for a thoroughgoing review of the framework legislation, the Secretary of State for Health and Social Care should give consideration to bringing within the scope of licensing any heritable genome editing interventions that currently fall outside that scope**.

Regulation

4.88 The UK has a regulatory system established by legislation, which means that something that is permissible in principle, under the law, is only permitted in practice if licensed by the HFEA (whose jurisdiction encompasses the four home countries). In this section, we refer specifically to the HFEA, although we hope that our recommendations may also be understood in ways that could apply equally to relevantly similar regimes in other jurisdictions.

4.89 The HFEA has discretion to develop regulatory policy to govern the exercise of its powers under the Act. This arrangement allows Parliament to set the parameters fairly broadly and the Authority to decide when appropriate conditions, such as those relating to the facilities and competence of licensees and the safety and efficacy of techniques to be used, can be met in practice. The expectation is therefore that, should legislation be made to permit heritable genome editing interventions discussed in this report, it will fall to the Authority to determine in what cases they may be used, as is presently the case with other techniques involving the manipulation of gametes and embryos. In assuming this role, we would expect the HFEA to take an approach to licensing similar to the one that it has taken with controversial applications of PGT and mitochondrial donation.

4.90 With PGT we have seen over time a measured expansion of the permitted range of uses as knowledge and techniques have developed and as patients have sought treatment for a greater variety of conditions.[529] Two established mechanisms have great importance at significant thresholds in this history. First, consultation with those who have an interest, usually described as 'stakeholders', has an important regulatory role in informing (although not determining) the HFEA's decisions. (In the case of questions touching on public morality, this can effectively mean open consultation with the public.) This procedure therefore potentially connects societal debate with the sites of decision making at the level of regulation. Second, the HFEA's decisions are subject to a prescribed internal appeal procedure and to independent judicial review on matters of public law, which means that the courts can be asked, by someone who has an interest who gives them appropriate standing, to determine whether a decision was one that the Authority was entitled to make and was properly made by the Authority (although not to challenge the Authority's judgment).[530] The decisions of the HFEA, as a public authority, are furthermore subject to the requirements of human rights law.[531] (While the relationship between human rights law and moral rights is complex and contested, we

[529] The process of adding new indications is driven, at bottom, by patients seeking treatment from a PGT centre, who will develop the appropriate test and apply to the HFEA to be allowed to use it in the clinic. Once a condition has been added to the list of authorised preimplantation genetic diagnosis (PGD) conditions, competent centres that hold an appropriate HFEA licence may then begin to carry out PGT for that condition; see: HFEA (2018) *Approved PGD and PTT conditions*, available at: https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/approved-pgd-and-ptt-conditions/. In some cases, and notably with mitochondrial donation, the Authority requires clinics to apply for a specific licence variation allowing them to treat named patients only.

[530] This happened, for example, when the public interest organisation Comment on Reproductive Ethics challenged the HFEA's power to license PGD with HLA typing; see: *Quintavalle (on behalf of Comment on Reproductive Ethics) v. Human Fertilisation and Embryology Authority* [2005] UKHL 28.

[531] The implication is that it would be reasonable – indeed required – for the Authority to disregard a clear indication of where the public interest in any decision before it lies that has been identified through consultation on the basis that acting in accordance with that indication would constitute a violation of human rights.

also make a further recommendation below about the orientation of the UK towards the international human rights project.)

4.91 If it is to regulate genome editing applications, the HFEA will need to establish appropriate procedures for considering licence applications and to determine the nature of any conditions to be applied to licences it may grant. A necessary condition of licensing must be that we are as sure as reasonably possible that the techniques are sufficiently safe for use in clinical treatment in a reproductive context. Although this is perhaps obvious, the question of how this should be determined is less so. The HFEA has considerable experience in these matters, which provides a sound basis on which to build. Therefore, **we recommend that genome editing should be licensed for clinical use only once risks of adverse outcomes have been assessed by a national competent authority (in the UK, the HFEA)**.

4.92 Nevertheless, as the HFEA's expert panel that reviewed mitochondrial donation techniques pointed out, "Research cannot answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time."[532] What is meant by terms like 'safe' and 'effective', while they might appear to be scientific criteria susceptible to research, in fact involve a considerable amount of judgment. For example, should the criteria for safety and efficacy be judged relative to the best available alternative treatment? While this makes sense in the case of therapeutic treatments (like new pharmaceutical products), in the case of reproduction the starting position is different. The question in this case may be posed in terms of how much risk it is reasonable to undertake in order to secure the birth of a child with the desired characteristics. Unlike with simple therapeutic treatment, however, the risks and benefits in this case do not primarily accrue to the same people. Thus, the welfare of the future person, the moral weight of the prospective parents' reproductive desires and the responsibilities of the various moral agents involved must be brought into consideration, in line with the 'welfare of the future person' condition that we set out in Chapter 3.

4.93 The welfare principle proposed in Chapter 3 has a stronger policy function than the licence condition applied by section 13(5) of the Human Fertilisation and Embryology Act 1990 since it guides both legislation and licensing policy. (Logically, if the envisaged procedure cannot, in any circumstances, be consistent with the welfare of the future person, then the law should not be changed. If, as we conclude, it is at least possible that some heritable genome editing interventions could conform with this principle and with the other principle that we identified in Chapter 3 – the principle of social justice and solidarity – then it is prudent to consider the realistic possibility of changing the law.) Likewise, if licensing a particular procedure does not conform with the principle, then no licence should be granted. In the present scheme, the Authority is required only to be assured (and, in effect, only after the fact) that the person providing treatment has taken account of the welfare of the child in order to fulfil this condition of their licence.

4.94 In proposing the principle in the previous chapter, we observed that the concept of welfare ('doing well') is a broader concept than well-being ('being well'; i.e. 'healthy') and its scope is, to an extent, socially and historically determined.[533] Scientific assessment

[532] HFEA Expert Review Panel (2016) *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update*, available at: http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/docs/Fourth_scientific_review_mitochondria_2016.pdf.

[533] This is exemplified by the way in which the original elaboration, which made 'the need for a father' part of this consideration, was revised in 2008 to refer instead to 'supportive parenting' (see: Human Fertilisation and Embryology Act 2008, s.14). In

can offer relevant information, but it supports rather than determines a much more complex requirement for judgment. Our discussion should have made clear how the different judgments that are proper to prospective parents, clinicians, regulators and Parliament forming an interrelated system in which each entails a different kind of responsibility and that, to be properly made, each requires different considerations to be taken into account. In the case of novel treatments, it is right that we proceed with extreme caution and that there are opportunities to reflect without prejudice in the light of experience and new information. Accordingly, if it is to be permitted, **we recommend that heritable genome editing interventions should initially be licensed on a case-by-case basis**.

4.95 If genome editing is eventually introduced into treatment, it will be important to monitor the consequences in practice. All licensed assisted conception treatments are registered, and we presume – as with PGT – that the HFEA would make Directions requiring the submission of information about cycles of treatment involving genome editing and record this on its statutory register of information. This would potentially allow the records to be used, subject to appropriate authorisation, in order to carry out research to identify long-term outcomes. However, the experimental nature of the technique is such that there is a need for planned and close follow-up of any families involved. It would also serve to trigger a moratorium should the need arise and inform the periodic review of the policy. While they cannot require people to consent to continuing participation and we are aware that there is a significant drop-out rate in ART follow-up studies, clinics can do a great deal to impress on families the importance of participating in follow-up of novel techniques and the benefit of doing so for themselves and for others. **We recommend that heritable genome editing interventions should be introduced only within the context of well-designed and supervised studies, reporting regularly to a national coordinating authority, and that the effect on individuals and society, including over generations, should be closely monitored as far as possible, compatibly with the privacy of the individuals concerned**.

Redesigning governance

4.96 The recommendations we have made above concern measures that could be given effect through existing institutional arrangements, at least in the UK. We believe that there are reasons to supplement these existing arrangements in certain ways.

4.97 We have noted the benefits of the current UK licensing regime. During our deliberations, we considered whether the HFEA was the right body to make licensing decisions on matters such as heritable genome editing interventions that were not principally about fertility treatment and fell into the Authority's remit only as a consequence of the fact that they involve assisted reproduction techniques. On balance, we concluded that it was appropriate to have an HFEA-type body carrying out the licensing function and providing oversight and monitoring of treatments. Though the field that the Authority regulates and its regulatory powers are organised in relation to the relief of medical infertility rather than the deliberate influencing of inherited characteristics, it has the capacity to draw on or develop the relevant expertise that it lacks and to adapt its conceptual frame as it has done in the case of PGT.[534] Thus, while we considered that there was an argument for

practice, the provision has been used with ambivalence at both a clinical and policy levels since 1991, such as arbitrarily to refuse treatment to single women, same-sex couples, non-traditional families, older patients, etc.; on the other hand, it has been argued that the reference to the welfare of 'any other child who may be affected by the birth' provides positive support for HLA typing to select donor embryos to treat affected siblings.

[534] The HFEA's guidance on PGD was developed initially though joint work with the Human Genetics Commission; see HFEA-HGC (2000) Outcome of the public consultation on preimplantation genetic diagnosis, available at:

research and genetic technologies that were not principally for the relief of medical infertility to be regulated separately, and under new and distinct legislation, on balance it makes sense for regulation to focus on the point that they must all pass through, namely licensed assisted conception centres, regulated by the HFEA.[535] Below, we consider two qualifications in relation to institutional support for societal debate and legislative provision for genetic discrimination.

The regulatory function of public debate

4.98 We have made recommendations above that recognise the importance of what we have called 'broad and inclusive societal debate' as a background to policy decisions about heritable genome editing interventions. As we have already indicated, 'broad' in this context means a debate that is not framed as a question about particular technologies, but considers the full range of responses to an identified challenge. The reason for this is to avoid an artificially narrowed and possibly distorted consideration. This can happen, for example, when a societal challenge becomes associated with a potential technological solution where other potential approaches, both technological and non-technological, might exist. Alternatively, it can happen when the nature of the challenge is understood from only one perspective that does not admit alternative constructions. A broad debate of this kind allows questioning of what is at stake (including what might be given up) in authorising and pursuing particular technological pathways and an exploration of different visions of future states of affairs and the values associated with them. Ultimately, such a debate puts into question ideas of the kind of common life that public policy exists to bring about, bringing shared and competing values to the surface. 'Inclusive' means that such a debate needs to attend to the views and values of all of those with an interest, not only those most directly and immediately affected, but also those who may be collaterally affected. In particular, it means attending to the voices of those who do not share the majority interest and who prospective technologies might place in positions of vulnerability, as well as creating opportunity to represent the interests of future generations, whose voices are necessarily absent. 'Societal' means that anyone subject to the jurisdiction has a legitimate interest in the debate to the extent that it engages the norms and therefore the conditions of common life by which they live. Nevertheless, any national decision to permit or prohibit heritable genome editing interventions will have implications beyond the jurisdiction in which it is taken (we address this below) but for reasons we have set out in the course of this report, we believe that it is permissible within a margin of appreciation for individual jurisdictions to decide these questions of principle. 'Societal' therefore means not universal, but orientated towards coherence at a national political level.

4.99 Our recommendation is also for 'debate' rather than 'consensus' (as some position papers on genome editing have recommended).[536] As with related matters such as IVF,

http://webarchive.nationalarchives.gov.uk/20081023093659/http://www.hgc.gov.uk/Client/document.asp?DocId=36&CAtegoryId=8. The Authority later developed guidance on preimplantation tissue typing, where an embryo is selected both to exclude a serious disorder and to include a tissue-type characteristic so that the resulting person can serve as a matched tissue donor for an affected family member.

[535] Except, of course, in the case of autologous engraftment of modified sperm precursor cells, as discussed above.

[536] See, for example: Baltimore D, Berg P, Botchan M, *et al*. (2015) A prudent path forward for genomic engineering and germline gene modification *Science* **348(6230)**: 36–8; Organizing Committee for the International Summit on Human Gene Editing (2015) On human gene editing: international summit statement, available at: http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a; Hurlbut JB, Jasanoff S, Saha K, *et al.* (2018) Building capacity for a global genome editing observatory: conceptual challenges *Trends in Biotechnology* **36(7)**: 639–41.

societal consensus is unlikely, although that does not mean that it is neither possible nor desirable to legislate.[537] In many ways, it is not so much achieving an endpoint that reconciles difference, but the fact that the position emerges from a broad and inclusive process that is important. While it is hard to imagine that genome editing could proceed without widespread societal support, the contingent outcome of debate should not be seen as determinative – it is appropriate that the decision rests with a properly constituted authority subject to requirements of international human rights law – or as final. Nevertheless, the idea of debate requires genuine engagement between different positions rather than simply measuring unreflective opinion and the distribution of prejudices. Our idea of public debate is also distinct both in conception and orientation from that of consultation on a specific question of public policy, of the kind that is used instrumentally to inform certain policy and regulatory decisions, although this has an important function. Debate, in the sense intended here, is about the mutual exploration of and engagement between values, interests and understandings, rather than about seeking answers to specific questions.

4.100 We have given some thought to how the kind of debate that we envisage can be fostered in practice and how it can connect to and inform the sites of public policy decision making. We favour an approach that lies partly in creating ways to link up existing interests and partly in providing opportunities and stimulus for interests to form, develop and be expressed through both uninvited and invited engagements. Attempts to foster and to harness this kind of debate in the past have met with different levels of success (regardless of what one thinks of the specific outcomes and their consequences).[538] Two well-known cases provide salutary examples to illustrate the challenges that such debates face. One is the public debate on the subject of genetically modified organisms in the early years of the present century (including activities organised by the UK government under the masthead *GM Nation?*). This has been picked over at great length by commentators; the salient point that we wish to emphasise, however, is the need to understand the multidimensionality of policy questions. This experience demonstrated starkly how mistaken the expectation that simply explaining the science clearly enough would lead people who were not part of the scientific and political culture to accept the outcomes that were valued within that culture.[539]

4.101 A second example is the public debate preceding the UK referendum in 2016 on membership of the European Union, which has also been extensively dissected, in which political elites in effect delegated a decision of profound public interest to a socially divisive process requiring no reflection or engagement.[540] In the first case, the engagement was largely unidirectional: the failure to agree was not a failure of understanding and no amount of information could repair the difference. In the second case, there was little genuine engagement between entrenched positions and the outcome was simply to reveal deep societal divisions without offering any process by which to bridge them. In neither case did the process nurture or consolidate the moral community, or help the members of this community engage with each other in trying to identify conditions under which they all should live. An important function of the debate

[537] In recent work that refers to the calls for engagement in genome editing, bioethicist Françoise Baylis has explored the notion of societal consensus in relation to strategies for collective decision making; see: Baylis F (2017) Broad societal consensus on human germline genome editing *Nature Human Behaviour* **1**: 0103; Baylis F (2016) 'Broad societal consensus' on human germline editing, *Harvard Health Policy Review* **15**: 19–23.

[538] See: Burall S (2015) *Room for a view: democracy as a deliberative system*, available at: https://www.involve.org.uk/2015/10/20/room-for-a-view/.

[539] This is effectively the view that had prevailed since the 'Bodmer report' (Royal Society (1985) *The public understanding of science*, available at: https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/1985/10700.pdf) and began to change after the report of the House of Lords Science and Technology Committee (2000) *Science and Society*, available at: https://publications.parliament.uk/pa/ld199900/ldselect/ldsctech/38/3801.htm.

[540] We say this without wishing to imply any view about the desirability of the UK leaving the European Union itself.

we envisage will be to give effect to the conclusions from the second division of Chapter 3, namely to gather up the interests of different publics into a contingent 'public interest' that could form the basis of developing public policy and to ensure that the interests of those potentially marginalised by social norms or placed in positions of vulnerability by the diffusion of new technologies receive adequate attention and protection in accordance with principles of social justice and solidarity.

4.102 It is clear to us, as we have said above, that this kind of debate cannot be fostered by a sector regulator, which would narrow it around the particular technologies within their remit. As we said above, it is important for the regulator to engage in consultation to inform regulatory decisions that raise issues of public interest. But this must be set against a background of debate that is significantly broader and capable of informing broader research and biomedical policy.[541] The measure of success of such an undertaking would not be providing solutions to particular questions and, much less, endorsing a particular preferred solution, but rather constituting a moral community through concrete forms of communication interaction and engagement in relation to a particular set of common problems.

4.103 Between the implicit and inchoate background of values and norms that pattern common social life and the explicit arguments surrounding distinct policy decisions, we consider that there is a need for an independent body that can help to join up the sites of uninvited dialogue and provide a 'clearing house' for public debate on the role of biomedical technologies in the future human composition of society.[542] This body might include the monitoring functions we have identified above to identify and amplify any emerging concerns about the impact of technologies on social equality and to track the development of societal norms. Therefore, **we recommend that consideration should be given to the establishment of a separate body or commission in the UK, independent of Government and independent of existing regulatory agencies, which would have the function of helping to identify and produce an understanding of public interest(s) through promotion of public debate, engagement with publics and monitoring the effects of relevant technological developments on the interests of potentially marginalised subjects and on social norms**.

4.104 We recognise that the establishment of a new body is an onerous recommendation and unlikely to find a warm welcome in the current political climate. Nevertheless, this is not a reason to shrink from pointing out the need to fill a significant vacuum or the reasons why it cannot be fulfilled by existing institutions. For over a decade, something like this role was fulfilled by the UK's Human Genetics Commission (HGC), which pioneered public engagement beyond unidirectional communication (providing information to the public through initiatives to promote the 'public understanding of science' or eliciting views from the public via consultation on predefined policy questions).[543] The HGC

[541] The distinction between consultation and debate should be clear here. Consultation may even be part of what it means for certain policy decisions to be 'properly made' and to help to insulate the Authority from judicial review.

[542] See: Burall S (2018) Rethink public engagement for gene editing *Nature* **555(7697)**: 438–9.

[543] Social and ethical concerns identified by the House of Commons Science and Technology Committee in its inquiry into genome editing (interrupted by the snap general election in 2017) included, "How ethical and social concerns relating to genomics are handled by the Government and UK health bodies, and whether a new body – akin to the Human Genetics Commission (which existed until 2012) – is required." House of Commons Science and Technology Committee (2017) *Genomics and genome-editing: future lines of inquiry*, available at: https://publications.parliament.uk/pa/cm201617/cmselect/cmsctech/854/854.pdf. This question was not picked up in the subsequent report, which gave only a cursory summary of the evidence received in relation to genome editing; see: House of Commons Science and Technology Committee (2018) *Genomics and genome editing in the NHS*, available at: https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/349/349.pdf.

convened a consultative panel of (initially) 100 people who were personally affected by genetic conditions and pioneered public dialogue to explore issues such as the forensic use of genetic information. It also maintained a number of monitoring groups, which kept in view and reported periodically on issues such as genetic discrimination, intellectual property, genetic databases and identity testing.

4.105 The kind of body we propose would bridge civil society and the clinical and research sectors. It would have links to government, rather than a single ministry, so as to be able to inform the development of public policy. It would also offer help to relevant regulatory bodies to inform regulatory policy on new genomic technologies. Its independent presence should help to nurture and sustain confidence that the public interest is being understood to encompass a broad and diverse range of interests and concerns that exist in civil society and is defined independently of the fertility sector and of scientific research. Importantly, and unlike existing national institutions, it should aim to engage with other countries and international institutions in the development of international norms.[544]

Discrimination

4.106 In this report, we have described the significance of increasing genetic knowledge in altering the epistemic position of prospective parents vis-à-vis their future offspring. Of course, this information is also potentially relevant, useful or exploitable for a range of other individuals, corporations and institutions. This possibility has led some countries to enact genetic anti-discrimination legislation. Although the UK has the advantage of national systems of healthcare largely through taxation (unlike private insurance-based systems in other countries), the relevance of genetic information is potentially much broader than health. There is currently a patchwork of arrangements (e.g. relating to workplace genetic testing and use of genetic test information in insurance) that is not rooted in statutory guarantees of protection.[545] Therefore, **we recommend, in the light of the potential for new forms of discrimination on grounds of genetic variation, that governments in the UK and elsewhere give fresh consideration to how these risks may be best addressed**. This should involve examination of whether more coherent, robust measures than the existing piecemeal, non-statutory mechanisms and arrangements are necessary or desirable**.** Such an examination might assess whether it is appropriate to treat genetic discrimination as a so-called 'protected ground' for the purposes of equality legislation or whether some other statutory prohibition supported by appropriate legal remedies might be preferable. Consideration should also be given to whether a more permanent and durable institutional framework is needed to provide

[544] The HGC was essentially a UK body (albeit covering the four home countries, genetics being a policy area reserved to Westminster in the devolution settlements), although it did have some dialogue with relevant bodies in other countries.

[545] The Information Commissioner's Employment Practices Code, for example, still recommends that employers "Inform the Human Genetics Commission of any proposals to use genetic testing for employment purposes" (despite the fact that that body was abolished in 2012; see: Information Commissioner's Office (2011) *The employment practices code*, available at: https://ico.org.uk/media/for-organisations/documents/1064/the_employment_practices_code.pdf). For insurance, see: HMG and ABI (2014) Concordat and moratorium on genetics and insurance (available at: https://www.abi.org.uk/globalassets/sitecore/files/documents/publications/public/2014/genetics/concordat-and-moratorium-on-genetics-and-insurance.pdf); NB. recommendations in the recent House of Commons Science and Technology Committee (2018) *Genomics and genome editing in the NHS* (Third Report of Session 2017–19) HC 349 (London: HMSO) that "The Government should set up systems to monitor any reluctance among patients to undertake genomic testing due to insurance concerns, assess the experiences of countries that ban insurers' use of predictive genetic test results (addressing in particular the ABI's concerns regarding the potential for adverse selection problems), and be ready to consider putting the Concordat and Moratorium on a statutory footing if the current voluntary system begins to limit the uptake of predictive testing." Such monitoring was previously carried out by the HGC, which received and reviewed an annual compliance report from the ABI and reported to ministers.

appropriate communication, information gathering, monitoring, enforcement and other functions in order to ensure that protection is meaningful and universally available.

4.107 There is one potential case of discrimination that arises as a possible consequence of arguments linking the enjoyment of human rights to the possession of an unaltered human genome. Though we have said (in Chapter 3) that we do not consider such arguments to be convincing or the asserted link to be meaningful, we nevertheless believe that, for the avoidance of any doubt, the possible corollary of this argument should not be permitted to result in discrimination against anyone who may be born following a heritable genome editing intervention.[546] For the avoidance of any doubt, therefore, **we recommend that governments in the UK and elsewhere give consideration to bringing forward an international Declaration affirming that people whose genomes have been edited should be entitled to the full enjoyment of human rights**. This might be achieved by bringing forward an international declaration to this effect, such as a declaration of UNESCO or by amending an existing declaration such as the Universal Declaration on the Human Genome and Human Rights.

Intellectual property and social justice

4.108 In Europe, including the UK, the patenting of "processes for modifying the germ line genetic identity of human beings" is prohibited.[547] No such ban applies to animals. In practice, this means that the application of such processes in animals can generate economic value, which might also inform the development of human interventions. Indeed, the opportunities for innovation in the field of enabling technologies and for 'CRISPR plus' innovations are considerable.

4.109 The recent and notorious CRISPR-Cas9 patent dispute between the University of California, Berkeley and the Broad Institute offers some insights into the possible use and misuse of patents.[548] Within the field of genome editing, disputes of this kind may have the consequence of impeding just the kind of innovation that patents exist to sustain and, while patents may empower inventors to control unethical practices, they may ultimately benefit narrow commercial interests more than the public interest.

4.110 Patent disputes between universities have been rare until now. Their first casualty is likely to be the research team: collaboration may be threatened by a breakdown in trust as faculty contacts are restricted and researchers avoid one another.[549] This is particularly problematic in the genomics and CRISPR fields because of their requirement for interdisciplinary and inter-institutional work (e.g. between molecular geneticists and computer scientists) and resource sharing.[550] The chill is apparent even between allies: although Jennifer Doudna and Emmanuelle Charpentier filed their joint CRISPR-Cas9 patent application in 2012, it was not until December 2016 that their respective institutions agreed a cross-licence.[551] Researchers may also become less frank about

[546] The instrumentalisation of cloned or genetically engineered people is a common trope in science fiction imaginaries.

[547] EC Directive 98/44 of the European Parliament and of The Council of 6 July 1998 on the legal protection of biotechnological inventions, Article 6(2(c).

[548] *Broad Institute, Inc. v. Regents of the University of California*., Patent Interference No.106,048, 2017 WL 657415 (P.T.A.B. Feb. 15, 2017).

[549] Sherkow J (2016) Pursuit of profit poisons collaboration *Nature* **532**: 172.

[550] Equipment costs are high. For example, a number of US institutions (including New York University, Columbia and Cold Spring Harbor Laboratories) share a suite of Illumina sequencers and staff (through the New York Genome Center) worth millions of US dollars. *The New York Genome Center purchases Illumina Hiseq X Ten sequencing system*, cited by Sherkow J (2017) Patent protection for CRISPR: an ELSI review *Oxford Journal of Law and Biosciences* **4(3)**: 565–76.

[551] CRISPR Therapeutics, Intellia Therapeutics, Caribou Biosciences and ERS Genomics announce global agreement on the foundational intellectual property for CRISPR/Cas9 gene editing technology. Caribou press release, 16 December 2016.

their work: Doudna's remark that her collaborators were not sure if CRISPR-Cas9 would work in eukaryotes became a key piece of evidence in the US patent interference case (in which the two claimants are contesting their priority as inventors of CRISPR-Cas9 as a technique to modify eukaryotes) and a warning to other researchers not to voice scepticism about their own work, contrary to the spirit of scientific inquiry. In a field so dependent upon the exchange of ideas and shared facilities, some feel that the CRISPR-Cas9 patent dispute is exerting a highly negative impact on the innovation required to deliver public or commercial benefit, the very opposite of the intended function of a patent. Furthermore, the cost of litigating such disputes is enormous. It is highly doubtful that the outcome of such disputes will be to the benefit either of the public or of scientific knowledge, and the process may draw on resources that might otherwise contribute to supporting excellent research.

4.111 The position may be further entrenched by the phenomenon of 'surrogate licensing' of patents, in which the licensing and commercialisation of a patent portfolio is outsourced from the university body to a third-party company that focuses on the field in question.[552] Both the US institutions involved in the CRISPR-Cas9 patent dispute have their surrogates: the University of California has passed its licensing operations over Doudna's patents to Caribou Biosciences, while the Broad Institute has passed operations to Editas Medicine. The effect is to put "a large and lucrative field for the exploitation of the licensed technology" in the hands of entities driven by duties to shareholders rather than to the public.[553] One consequence of surrogate licensing may be 'bottlenecking', in which a surrogate grants exclusive licences that are broader than the licensee requires, without a right to sub-license, thereby effectively preventing a field from being developed by others until expiry of the 'head' licence.[554] A surrogate may also be motivated more by its commercialisation role than by its licensing function, which can work against technology distribution: when potential licensees are also potential rivals, smaller enterprises may be placed at a negotiating disadvantage compared to those with larger portfolios and cross-licence opportunities, a tendency that may consolidate IP among larger institutions. Again, this runs counter to the presumed function of patents as instruments of public benefit.

4.112 Despite this, CRISPR-Cas9 patents can be used in socially positive ways. A patent is a negative right that gives inventor patent holders a power to exclude others from exploitation of the patented technology as, for example, in connection with gene drives.[555] The power is limited by the normal 20-year lifetime of the patent, but this may be sufficient for governance, including statutory controls and regulation, to form around the technology and establish scientific and ethical oversight. During the life of the patent, its owner may use licences to promote access: for example, Monsanto's licence from the Broad Institute in connection with various agricultural applications "requires Monsanto to allow its farmer customers to save and resow seed from one season to the next, in contrast to some of Monsanto's past practices."[556] Assuming the underlying patents have not expired by the time that any CRISPR-Cas9 human interventional products or services are commercialised, patent holders can publicly refuse to enforce patents against

[552] As distinct from a university's general technology transfer office.
[553] Contreras JL and Sherkow JS (2017) CRISPR, surrogate licensing, and scientific discovery *Science* **355(6326)**: 698–700.
[554] ibid.
[555] Possible objections to this approach may be raised on the basis of non-exploitation. This report does not consider compulsory licensing, but we suggest that such a discourse should also consider aspects of *ordre public* and morality in those jurisdictions in which Article 27(2) of TRIPS applies. On gene drives, see: Yong E (2017) One man's plan to make sure gene editing doesn't go haywire *The Atlantic* 11 July.
[556] Sherkow J (2017) Patent protection for CRISPR: an ELSI review *Oxford Journal of Law and Biosciences* **4(3)**: 565–76, citing Guerrini CJ, Curnutte MA, Sherkow JS, and Scott CT (2017) The rise of the ethical license *Nature Biotechnology* **35(1)**: 22–4.

researchers or institutions and could, in theory, impose price control and access requirements in connection with therapeutic applications.[557] Despite the benign possibilities inherent in ethical licensing, we have nevertheless already observed the difference in ethical views between states, to which patent holder discretion provides an empty remedy. Therefore, **we recommend that governments in the UK and elsewhere should monitor and give consideration to the use of intellectual property rights in order to promote the public interest in having safe, effective and ethical heritable genome editing interventions**. The outcomes of such consideration might be that governments and public research and healthcare institutions could adopt a policy of non-enforcement within the home state of relevant patents (and rights in associated software and databases) arising as a result of research funded wholly or in the main by that state. Relevant bodies (such as UK Research and Innovation and the Department of Health and Social Care in the UK) might also consider the desirability of securing coordinated group licensing arrangements to facilitate research and innovation. The monitoring and advisory function that we suggested in our recommendation could be fulfilled in the UK by the new body that we have recommended should be established.

Broadening dialogue

4.113 We believe that international institutions have an important role to play as venues for international dialogue and also for cross-cultural ethical debate. These include international industry organisations, international human rights institutions, interdisciplinary academic collaborations and INGOs.

International dialogue

4.114 Regional and international industry organisations such as the European Society of Human Reproduction and Embryology, the European Society of Human Genetics and the International Society for Stem Cell Research sponsor international conferences that provide venues for exchanges predominantly among scientists and clinicians working in different countries. They often also involve those working in related academic disciplines that study or reflect on research and biomedicine, such as the social sciences and medical ethics. Many have ethical initiatives that engage participants with backgrounds outside the most relevant scientific and clinical fields. Such organisations often establish and produce position papers that usually reflect the interests of the membership (albeit that those may include interests in ethical research and practice).[558]

4.115 *Ad hoc* initiatives like the National Academies summits, which are driven by scientists who wish to engage at an international level with other disciplines and stakeholders, also provide venues for international dialogue.[559] A new interdisciplinary initiative is the Association for Responsible Research and Innovation in Genome Editing (ARRIGE. This began as an initiative under the aegis of the French medical research institute, Inserm, reaching out to those involved in research governance in other parts of the world (notably

[557] ibid.

[558] See, for example: de Wert G, Pennings G, Clarke A, *et al*. (2018) Human germline gene editing: recommendations of ESHG and ESHRE *European Journal of Human Genetics* **26(4)**: 445–9.

[559] The joint initiative of the US National Academy of Sciences and National Academy of Medicine, the UK's Royal Society and the Chinese Academy of Sciences held an initial summit in the US, in Washington, DC, in December 2015. A further summit is planned for Hong Kong in November 2018.

South America, India and Africa).[560] It has since taken a new shape as an independent association of participants from over 35 countries and from a range of disciplines.[561] It is too early, at the time of writing, to tell whether it will fulfil the ambition to become a key international forum and whether it will move away from the research perspective with which it began and succeed in giving effect to critical RRI practices, including the orientation of research purposes by societal goals and values.[562]

4.116 The call for 'broad societal consensus' that was taken up by the first National Academies summit has been given further shape by an interdisciplinary group of scholars and researchers who have proposed the establishment of a 'Global Genome Editing Observatory'.[563] Part of the ambition of this initiative is to overcome cultural divisions, both those between national cultures (hence the 'global' ambition) and between disciplinary cultures (and particularly the asymmetry that has meant that the agenda was initially shaped by those with an interest in advancing the research).[564] To achieve this, a new infrastructure is proposed comprising an international network of scholars and organisations.[565] Its functions would be to act as a global clearing house for existing positions, to track conceptual developments, emerging tensions and points of consensus (and also to locate them as boundaries on the geo-ethical map), to identify power asymmetries and the exercise of influence, to bring into contemplation different visions of common life and to provide a vehicle for international meetings.

4.117 This proposal is animated by a contemporary ideal of cosmopolitanism that respects difference (that there is more than one valid and relevant way to analyse what is at stake in the application of technology) and aims to make progress towards wider, more reflective agreements about ways of living in the shared world (rather than unearthing a universal form of morality).[566] It is designed to produce the kernel of a moral community at a global scale around genome editing. While it remains to be seen whether such an initiative could produce a consensus that is sufficiently broad or strong, for example, to secure an agreement "not to proceed with some research until a more equitable approach to setting the terms of debate is achieved," it could nevertheless provide a much needed counterbalance to globally divisive technonationalism and help to orientate discussion of policy towards the human purposes and consequences of technological change and technology transfer. We therefore endorse the desirability of monitoring and promoting dialogue among nations in a way that recognises and attends to the diversity of voices within each nation and that may be furthered by support for and participation in a dedicated global observatory or international association, as well as through the work of international institutions.

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[560] Chneiweiss H, Hirsch F, Montoliu L, *et al*. (2017) Fostering responsible research with genome editing technologies: a European perspective *Transgenic Research* **26(5)**: 709-13.

[561] See: www.arrige.org.

[562] For RRI, see: Owen R, Macnaghten PM, and Stilgoe J (2012) Responsible research and innovation: from science in society to science for society, with society *Science and Public Policy* **39(6)**: 751–60.

[563] This proposal originates from an interdisciplinary workshop held at Harvard University in the spring of 2017. The workshop, under the rubric 'Editorial aspirations: human integrity at the frontiers of biology', was organised under the aegis of the Harvard Science and Technology Studies programme by Sheila Jasanoff, Ben Hurlbut and Krishanu Saha (see http://sts.hks.harvard.edu/events/workshops/editorial-aspirations/). Participation was international, although predominantly from the US, and largely academic, but the range of disciplines and perspectives and the level of engagement between them were notable and refreshing.

[564] The proposal is outlined in: Jasanoff S and Hurlbut JB (2018) A global observatory for gene editing *Nature* **555**: 435–37; and developed in: Hurlbut JB, Jasanoff S, Saha K, *et al*. (2018) Building capacity for a global genome editing observatory: conceptual challenges *Trends in Biotechnology* **36(7)**: 639–41.

[565] Saha K, Hurlbut JB, Jasanoff S, *et al.* (2018) Building capacity for a global genome editing observatory: institutional design *Trends in Biotechnology* **36(7)**: 639–41.

[566] See: Appiah KA (2006) *Cosmopolitanism, ethics in a world of strangers* (London: Penguin Books), which owes much to cultural anthropology, unlike the more naturalistic ideal of Enlightenment cosmopolitanism.

Developing international human rights law

4.118 A global alignment of governance in this area at anything other than a rather abstract level would be a challenging objective. In our view it is, however, also unnecessary and may be undesirable, particularly if it were to lead to the adoption of a 'lowest common denominator' approach. There is no agreement internationally, for example, on the status of the human embryo, on germ line modification, on PGT or gamete donation; where there is agreement in terms of the outcome to be achieved, it is often for different and sometimes incongruent reasons.[567]

4.119 A number of states have not developed measures to govern human genome editing or do not have existing measures that would apply to it. This risks making them unwilling or unwitting magnets for those who wish to evade national regulatory controls or, at the very least, makes it difficult to be certain of the conditions (including ethical conditions) under which research or (potentially) clinical interventions are carried out. For many countries that do not have domestic provisions, international organisations such as the Council of Europe of UNESCO provide welcome guidance and off-the-shelf standards and legislation. Common standards also help to facilitate the transfer of knowledge, practices and technologies. Differences (including ethical differences), on the other hand, can result in gradients along which people and resources flow, as we have noted above. Whatever the UK's position, prospective patients and practitioners will either come here or, if conditions are unfavourable here, find their way to other jurisdictions that are amenable to the practices in which they wish to engage.

4.120 The international human rights framework provides a common guard rail that allows a margin of appreciation but not a complete free-for-all, although it is as yet underdeveloped in relation to the cases of the heritable genome editing interventions we have discussed. The point at which the UK is moving away from EU institutions might not seem like an auspicious one to engage more closely with the European human rights project. Nevertheless, the UK aspires to be a world leader in life sciences, which depends substantially on international exchange to secure the benefits projected in its own industrial strategies. It is therefore natural that it should engage more closely in the discourse that provides globalisation's moral conditions of possibility.

4.121 At a political level this is finely balanced and has implications for scientific collaboration, healthcare, international trade and services, and repercussions in many other fields.[568] As a result, issues such as the acceptability of heritable genome editing interventions risk being caught by the undertow of deeper currents of political engagement and identification. The UK walks a difficult path; it can distance itself from the international community, which also potentially means exacerbating ethical gradients that may obstruct the flow of knowledge and technologies, or strive to be a leading participant in

[567] For example, the basis of alleged 'consensus' on the Biotechnology Directive.

[568] When the Government has been asked why it would not sign the Oviedo Convention in the past, the reason given has been to do with domestic legislation in progress, often relating to the devolution settlements. These reasons have now largely evaporated. For example, on 23 March 2015, in response to a question from Lord Patten (HL5536), Earl Howe, then the Parliamentary Under-Secretary for the Department of Health, answered: "The Council of Europe Convention on Human Rights and Biomedicine covers a very wide range of complex ethical and legal issues. These issues involve a large number of different policy areas which are covered by a mixture of United Kingdom legislation and common law and some of the relevant policy areas are within the competence of the devolved administrations. In common with a number of other European Union states, the UK has not signed or ratified the Convention." This suggests a policy shift from the position implied in an earlier response to a similar question (HL65) in June 2014, which suggested that signing was a long-term objective: "As previously stated, in the United Kingdom, the complex nature of devolved responsibilities in this range of policy areas has delayed consideration of full ratification. In the meantime, the UK continues to take an active role in Council of Europe negotiations and development of relevant protocols."

international research and governance but accept that its obligations may potentially slow domestic advance. We have concluded that the societal challenges, priorities and acceptable practices should be determined at the level of national jurisdictions, but nevertheless within a margin of appreciation that is reasonable under developing international human rights law. The process of elaborating this requires international dialogue and collaboration at many levels and between these levels. Therefore, **recommend that governments in the UK and elsewhere should work with international human rights institutions such as the Council of Europe and UNESCO to promote international dialogue and governance with regard to heritable genome editing research and innovation**.

Conclusion

4.122 The UK is not starting with a blank slate when it comes to the governance of heritable genome editing interventions. The activities involved are already subject to obligatory licensing and regulation under the Human Fertilisation and Embryology Act 1990.[569] A range of other provisions (e.g. to do with quality and safety, control of therapeutic products and professional conduct) are also in place. Many of these derive from EU legislation. In addition, many instruments of soft law and governance provide further definition and guidance, and these enjoy a high degree of compliance in what is, in most cases, a field with a cohesive academic and professional culture. It is primarily in this space that the debates about novel possibilities raised by genome editing have been taken up to date: among research organisations, professional bodies, parliamentary committees, government officials, regulators and NGOs. These debates are not, therefore, about establishing governance of genome interventions from scratch, but about the controlled and reasoned modification of restrictions already in force.

4.123 The UK occupies a place within a wider system of EU, regional and international law that permeates and underpins its relationships and dealings with other states, not only in the field of biomedicine, but also as a member of an international community committed to upholding and advancing human rights. Though this system tolerates margins of appreciation, which permit the expression of differences in prevailing societal values, it maintains a measure of international coherence while respecting these differences. For states that do not enjoy nationally elaborated governance systems like that of the UK, these provide an external structure and orientation.

4.124 Just as governance does not lack a framework, background and history, the public meaning and interest in genome editing is not uninformed. There have been rich and relevant debates in the past on issues such as IVF, GMOs, PGT, etc., which have informed prevailing societal norms. The pitch of public debate changes in response to developments, and public attention comes and goes, but, though cultural understanding is latent, it is not absent. The moral community exists implicitly and diffusely. Its resources are the implicit system of interrelated norms (the 'moral fabric of society') and the social meanings of technologies in play; these may only become explicit, and implications and tensions among them emerge, when attention is focused on a question of immediate importance. Because an issue often only becomes salient and (beyond permanent interest groups) publics only take shape once a concrete policy question is to be decided, the distance to travel between the implicit norms and explicit policy is all too evident, and the opportunities to take in the surrounding landscape on the way are

[569] This is the case for all procedures that we have envisaged except, arguably, in the case of modification and engraftment of autologous spermatagonia, as noted above.

limited. The very circumstances in which such policy questions arise are usually too narrow and too late to allow critical reflection on alternative courses or destinations.

4.125 If the UK were to relax the restrictions currently in force, it is against this background of norms, values and understandings that this must take place. Three processes support this: the constitution of publics in relation to the questions of public interest (organisation), the production of the 'public interest' out of the interest of different publics (engagement) and the connection of expressed public interest with the sites of decision making (democracy). The first of these requires that the issue is raised to public salience, but investing resources in this is only mandated if it is an issue of public interest. Who decides this is important. The second enjoins a deliberative process, one that is reflective and that engages publics with each other rather than segregates them into groups 'for' and 'against'. The third depends on the political organisation and procedures of states, but not only formally: also important are informal processes of consultation, influence, patronage, activism, etc., that are established in the society.

4.126 There is a need to engage continually in order to produce a public interest not just around pressing questions of policy, but also around critical questions of commitment to values governing selection, innovation and diffusion of technologies. This engagement has an important regulatory function – it should be broader and earlier than questions of the permissibility of particular technologies and it should be capable of influencing the agenda, discovering which questions are important and influencing how they are framed. This cannot be left solely in the hands of a sector regulator, but requires institutional support that embodies the recognition that technologies diffuse, embed and shape common social worlds.

4.127 The discernment of public interest is distinct from the important and specialised role of regulation. We find that decisions about the licensing of interventions permitted in law should be reserved to a national competent authority (in the UK, the HFEA). Relevant considerations face in two directions: towards the clinics (whether the procedure is safe and competently handled) and towards the public (whether the procedure is one to which people ought to have access). The former question is properly informed by expert opinion, but it is not a question that can be resolved by expert opinion ('safe enough' is not an analytical judgment). We have made a small number of operational recommendations for the HFEA about licensing procedure and conditions of licences. The latter question relates to reproductive aims and the welfare of the future person. Where this concerns decisions about extending the range of characteristics that may be edited, the HFEA should have regard to the public interest (to inform decisions through consultation and engagement), and its decisions should be (as they are) amendable to judicial review (which provides an opening for human rights considerations to come to bear).

4.128 As regards the gap between the implicit moral fabric of society and the need to address specific questions of policy, we find that further efforts are required in two directions. The first is contributing to the development of the international human rights framework. The second is sustaining a community of public interest around biomedical science and technologies and the common challenges they address. In times where emerging social divisions present new challenges domestically and internationally, we believe yet more efforts are required to promote the coherence of the domestic moral community under governance and subject to laws and to maintain workable moral gradients between jurisdictions, balancing incentives to achieve the benefits new technology undoubtedly promises with a commitment to global justice and solidarity.

Chapter 5

Conclusions and recommendations

Chapter 5 – Conclusions and recommendations

Chapter 5 overview

The final chapter draws together the conclusions and recommendations from the report, setting these out in a concise summary of the overall line of argument.

5.1 The terms of reference for the project invite the working party, having examined the ethical questions and reviewed existing provisions, "to report on these matters and to make recommendations relating to policy and practice." It is to be expected that perhaps the main question in which readers of the report will be interested is whether we conclude that there are circumstances in which genome interventions to influence inherited characteristics should be permitted in humans. **We can, indeed, envisage circumstances in which heritable genome editing interventions should be permitted**.[570]

5.2 These circumstances do not obtain at present. We believe, however, that there is a real possibility that they could obtain in the future. We believe that the current trajectory of development, the dynamics of which have both technological and social aspects, makes this increasingly likely, although by no means certain. Although our report identifies circumstances in which genome interventions of this sort should not be permitted, we do not believe that there are absolute ethical objections that would rule them out in all circumstances, for all time. If this is the case, **there are moral reasons to continue with the present lines of research and to secure the conditions under which heritable genome editing interventions would be permissible**.

5.3 It is inevitable, given the nature of the intervention, that these conditions should be exacting. They will depend on developments of scientific knowledge, clinical technique, moral norms and organisational practices, the unfolding of social processes and the institution of regulatory measures, among other things. The aim of this report as a whole is to identify the most important of these conditions and suggest how they might be secured.

5.4 We were aware that, in thinking about the wider influence of our work, we should consider both the 'conceptual' influence as well as the 'instrumental' impacts this report may have.[571] Our report contains many conclusions that we hope will have conceptual significance concerning how we should think about the prospect of heritable genome editing interventions, what they will mean for people and societies, and in what context

[570] It should be clear from reading this report that it is a mistake, though one that is quite common in the literature on this subject, to focus mainly on the *instance* (the nature of the genetic characteristic to be excluded or included; a serious disease trait, for example). The *circumstances* in which heritable genome editing interventions take place and the principles with which they should conform are crucial. Whether any instance is morally acceptable depends less, in our view, on the characteristic in question than on the circumstances that make it right to assist prospective parents, evaluating their interests in having a certain kind of child in the context of the approaches and technologies available and the direct and indirect consequences of this for all those it affects, including its implications for the complex system of norms that governs the moral community.

[571] Outputs may be used instrumentally as evidence in evidence-based policy making, for example; conceptual impacts are more subtle and are largely concerned with bringing issues to salience, with how we think about those issues and with investing them with meanings, even to the extent of making them appear or disappear as issues to be addressed. It is recognised in the literature that while 'conceptual impacts' are less demonstrable than 'instrumental uses', they are not less important.

questions about them should be posed. It also contains some practical recommendations about measures that different bodies might take to secure the proper moral appraisal and control of any proposed heritable genome editing interventions.

5.5 Although our report is not about any particular genomic technology and not principally about technology at all in any narrow sense, undoubtedly the development that provoked our inquiry was the invention of CRISPR-Cas9 genome editing systems. The application of CRISPR-Cas9 in mammals was first reported in 2013. Since that time, the system has been refined and repurposed to allow higher-fidelity genome editing, including base editing, as well as epigenome editing.[572] Genome editing by CRISPR-Cas9 can, in principle, result in a broad range of genome changes. However, it is as yet not known how to harness the cellular machinery required to repair genome breaks made by CRISPR-Cas9 with sufficient efficacy for clinical applications. Epigenome editing, which does not cut the genome, is still at an early stage, and its clinical potential is still being explored. Base editing, which also does not produce genome breaks and makes changes that are restricted but precise in nature, may already be safe enough for clinical evaluation. We conclude that, if this field continues to advance at its present rapid rate, **it is likely that different CRISPR-Cas9 technologies will be clinically safe in the foreseeable future**.

5.6 We have striven to set these developments in a broader dynamic context to illuminate the interplay between the social, political and economic drivers and constraints that influence them. In particular, we have tried to illuminate how advances in genomics and reproductive technologies can focus the interests and responsibilities of individuals and society on particular 'problems' that are formulated in novel ways and on particular interventions that might address them. In Chapter 1, we acknowledge the significance of the growing background of genomic knowledge, both about the consequences of genomic variation generally and the knowledge that people have about their own genomic endowment. This brings a new layer of complexity to how people understand their own embodiment in relation to inherited characteristics, particularly those that are associated with states of health and disease. In view of this, **we support the need for initiatives on the part of health policy research organisations to explore ways in which genetic counselling capacity, public education and the provision of trustworthy information to the public about genetic conditions could be increased**.

5.7 We examine the possible aims of heritable genome editing interventions, noting how they might help people to achieve their goals to have a child who is genetically related to them and who has or does not have characteristics associated with a genetic variation that they could pass on. The clearest cases we consider are those associated with inherited genetic disorders, where the inheritance pattern and outcome for the offspring are well characterised. We set these goals in the context of other courses of action that people in this position might take to become parents (including those that allow them to become parents but with only a partial or no direct genetic connection to their child). Although we recognise that the desire to have children itself is profound and personal, the context created by prior genomic knowledge and the available reproductive technologies can lead to a more deliberate choice of the means of achieving it. **Our question can be summarised as: in what circumstances, in what ways and to what extent should people be permitted, enabled and assisted to pursue their goals?**

[572] The differences between these techniques and how they might be used in clinical situations are discussed in Chapter 2.

5.8 From the situation of people facing possible reproductive decisions, we turn in Chapter 2 to focus more closely on the new genome interventions that could become available to them. In particular, we consider the emerging technologies of genome editing and the enabling knowledge and technical achievements that will be required for them to become clinically feasible options. We also emphasise the importance of factors driving the development of these technologies, including the scientific, technological and social drivers, as well as the moral, political, legal, regulatory and economic conditions that may impede or facilitate this development. We foresee ways in which, as these conditions develop, genome editing might enter into clinical use, initially in rare and hitherto intractable cases of inherited genetic disease or predisposition to serious disease, but thereafter potentially in a wider variety of circumstances. We consider the factors that are most likely to restrict, control or divert this technological diffusion, including the availability of alternative courses of action and national laws and other regulatory constraints rooted in prevailing moral values. Looking ahead, if the demonstration of an acceptable level of safety and reliability is achieved, we conclude that **genome editing has the potential to give rise to transformative technologies in the field of human reproduction**.

5.9 In Chapter 3, we proposed a way of appraising the moral significance of the various interests that are invested in heritable genome editing interventions and of identifying the nature of the responsibilities that pursuing these interests entail. The approach that we propose makes use of the accessible and internationally recognised language of human rights (important given the international scope of the technologies), which is relatively easy to translate into legal and regulatory measures. This approach allows us to bring into the appraisal something that is rarely examined: namely, the moral weight that is implicitly given to prospective parents' interests in having children with particular characteristics. (Such characteristics might include being directly genetically related to the parents and not having – or having – a specific inherited genetic condition.) Although we do not find an ethical reason to regard these interests as good in themselves, we note that they are commonly given significant moral weight. Our approach allows us to recognise that the interests of the prospective parents are not the only ones that are relevant, however, since their actions inevitably affect the conditions of life of others. It allows us to consider how the other relevant interests qualify the parents' moral entitlements to take up various options that might be available to them: their rights not to be prevented by others and, potentially, to be assisted by others in pursuing their goals.

5.10 We consider first the interests of those directly involved (the prospective parents and their potential offspring). Because these interests are both interdependent and formed in particular socio-technical contexts, we conclude that a judgment about the acceptability of a course of action cannot be based simply on an estimation of the probability of different outcomes and some description of the condition or characteristics to be avoided (or secured). On the other hand, we conclude that the relationship between the prospective parents' aims and the welfare of the future person they aim to conceive must be a constant and central consideration. We therefore propose a principle that negotiates a route between two positions that have been argued in the relevant literature. The first is the position that the welfare of future people does not matter at all (so long as the future person has a life that is worth living); the second is that it matters in a way that is too demanding or constraining for prospective parents (requiring speculative attempts to secure the best life possible for their child or mandating eugenic interventions).

Principle 1: The welfare of the future person

Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.

5.11 Assessing whether heritable genome editing interventions can conform with this welfare principle requires at least that further biomedical research is undertaken to assess, so far as possible, the nature and likelihood of any safety risks and to improve the efficacy and specificity of the techniques. Although this can only provide assurance up to a point, it is important that all the research that can illuminate these questions is concluded before any specific move into clinical use is authorised. We therefore conclude that **research into the safety and efficacy of genome editing techniques should be undertaken and supported in the public interest in order to inform the development of evidence-based standards for clinical use**.

5.12 Though necessary, biomedical research is not, on its own, a sufficient basis for assessing the likely welfare implications of genome interventions on future people. In our view, the concept of welfare extends beyond a purely medical description (so a medical/non-medical distinction cannot satisfactorily delineate acceptable uses of genome editing). Furthermore, the concept is highly dependent on the circumstances in which the future person will live. We therefore conclude that **social research that would help us to understand the welfare implications for people born following heritable genome editing interventions (e.g. involving people born following preimplantation genetic testing) should also be supported in the public interest**.

5.13 The interests of prospective parents and their offspring are not the only morally relevant considerations, however. Other people may also be affected collaterally, but because the effects on them are less immediate and more diffuse, they are often overlooked, even though they may be of greater consequence in the longer term. Individual acts take place within the context of societies and moral communities that are governed by systems of interrelated norms. These norms can take a variety of forms, such as formally codified as laws, embodied in customary practices or understood as implicit rules of morality. They govern how all people in the moral community are treated, but they become especially important when certain members of the community find themselves in positions of vulnerability because of the collateral or unintended effects of a particular development. Alongside the first principle relating to the 'welfare of the future person', we posit a second principle to account for this.

Principle 2: Social justice and solidarity

The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.

5.14 Norms are not immutable, however, but may respond and adapt in the light of developments (including those in science and technology) through a process of collective

moral reflection. In fact, the moral and social concerns of society and the goals of its science and industry can be seen as co-determined. Like the 'welfare of the future person' principle, which it complements, the 'social justice and solidarity' principle requires further elaboration to show how it can be given effect in practice. This may also be illuminated by research, but the way in which it is made explicit requires a prior process of reflection and deliberation, since norms do not relate only to discrete biotechnologies, but are rooted in shared values and form an interrelated system. We conclude, therefore, that **heritable genome editing interventions should be introduced only after there has been a sufficient opportunity for broad societal debate**.

5.15 Among the potential collateral effects of heritable genome editing interventions are increased marginalisation or stigmatisation of those who have or do not avoid certain heritable conditions. It is therefore particularly important that the voices of people who may be collaterally affected are attended to and that they are not obscured by a focus on the goals of prospective parents or by the aggregation of opinions around decision points constructed to distinguish majority and minority opinions rather than seeking a constructive engagement between different points of view. We conclude, therefore, that **efforts are needed to engage in open and inclusive consultation with those whose vulnerability to adverse impacts might be increased by the introduction or extension of heritable genome editing interventions.**

5.16 As well as the impact on people's interests and their conformity with shared moral norms, we also considered heritable genome editing interventions from the point of view of abstract moral principle. We considered the claim, made by some, that editing the genome of one's descendants might amount to an infringement of human dignity. We do not find the concept of human dignity helpful in this context. In our view, what is morally important about human beings is not dependent on the possession of a particular set of genomic variations: we find the concept of 'the human genome' to lack coherence in any case. We conclude that **so long as heritable genome editing interventions are consistent with the welfare of the future person and with social justice and solidarity, they do not contravene any categorical moral prohibition**.

5.17 Given our conclusions that heritable genome editing interventions may be morally permissible in certain circumstances, in Chapter 4, we turn to the subject of their governance. We make four sets of more specific recommendations: for research organisations, governments in the UK, governments generally (in the UK and elsewhere) and licensing and regulatory bodies. Collectively, these are intended to help give effect to the two principles we identified in Chapter 3 (the 'welfare of the future person' principle and the 'social justice and solidarity' principle).

5.18 In parallel with encouraging public debate, there is a need to continue to support scientific research into safety and social research into the potential wider effects of heritable genome editing. Because this research is in the public interest, there is reason to fund it publicly, although subject to the determination of wider funding priorities. Ideally, this research should be well coordinated and the findings placed in the public domain. Public and charitable funding bodies (among them, for example, UK Research and Innovation and Wellcome) have the opportunity to play an internationally leading role in this.[573]

[573] See below for our recommendations regarding commercial organisations and patenting.

Recommendations for research bodies

Recommendation 1 **We recommend that research to establish the clinical safety and feasibility of genome editing should be supported in the public interest in order to inform the development of evidence-based standards for clinical use**

Recommendation 2 **We recommend that social research that would help to understand the welfare implications for people born following heritable genome editing interventions (e.g. involving people born following preimplantation genetic testing) should also be supported in the public interest**

5.19 We surveyed the current situation in a variety of jurisdictions, as well as the relevant provisions and measures of international law. The genome interventions that we have discussed are provided for – and currently prohibited – by law in the UK, although not explicitly. We have identified one case that, although somewhat obscure, may fall outside the scope of the current HFEA licensing regime and may be desirable to bring within the regime. This is the case of the autologous transplantation of modified gametes from stem cells or gamete precursor cells, or the autologous engraftment of gamete-producing tissues or organoids. If necessary, this could be remedied by extending the scope of legislative provision through regulations under section 1(6) of the Act. In countries other than the UK, we find that there is a wide variety of different approaches that are rooted in their different histories and cultures, some of which are likely to be more receptive to heritable genome editing than others. **We find that there is no provision of international law, however, that would prevent the UK or another country from authorising heritable genome editing interventions in the way that we envisage this might occur**.

5.20 We conclude that any amendment of domestic legislation should be broached in the context of a thoroughgoing review of the appropriateness of the present regulatory approach, including the role of the HFEA. Before any change in the law is brought forward, we think there will be a need both for prior impact assessments and to put in place arrangements for continuing monitoring, as well as mechanisms to ensure that, if permission is given, it can be withdrawn should circumstances change. **No change in the law to permit heritable genome editing interventions should be broached, in any case, without consideration of whether it can be ensured that any proposed use would conform to the principles we have set out in this report** (the principle of the welfare of the future person and the principle of social justice and solidarity).

5.21 Given the pace of developments in the underlying research, we believe that there is a need to begin to engage the public with these questions and that this should happen without delay. **We conclude that there is a need for a body in the UK that is independent, well resourced and not time limited to promote societal debate on these and related matters**. We conclude that an independent body would be preferable to these functions being carried out by Government, which is unlikely to be able to sustain the function over time, or by the HFEA, given its licensing and regulatory function, the importance of its relationship with the sector and its limited resources. An independent body, perhaps on the model of the Human Genetics Commission or the Royal Commission on Environmental Pollution, would help to give public confidence and to provide a focus and site for the development of public interest. It would bridge civil society and the clinical and research sectors and have links to Government so as to be able to

inform the development of public policy, as well as to the HFEA to inform regulatory policy on new genomic technologies. Importantly, and unlike existing national institutions, it should aim to engage with other countries and international institutions in the development of international norms.

Recommendations for UK Government

Recommendation 3	**We recommend that, before any move is made to amend UK legislation in order to permit heritable genome editing interventions, there should be sufficient opportunity for a broad and inclusive societal debate**
Recommendation 4	**We recommend that, without awaiting the opportunity for a thoroughgoing review of the framework legislation, the Secretary of State for Health and Social Care should give consideration to bringing within the scope of licensing any heritable genome editing interventions that currently fall outside that scope**
Recommendation 5	**We recommend that heritable genome editing interventions should be permitted only provided that the impact on those whose vulnerability to adverse effects (including stigmatisation and discrimination) might thereby be increased has been assessed and mitigated (and, in any case, not without open and inclusive consultation with people in those positions)**
Recommendation 6	**We recommend that heritable genome editing interventions should only be permitted provided that arrangements are in place to monitor the effects on those whose interests may be collaterally affected and on society more generally, and provided that legitimate and effective mechanisms are in place to redress those effects and to revise relevant policy; this should include a clear regulatory measure to trigger a moratorium and a sunset provision, requiring review and an affirmative resolution to permit the practice to continue**
Recommendation 7	**We recommend that consideration should be given to the establishment of a separate body or commission in the UK, independent of Government and independent of existing regulatory agencies, which would have the function of helping to identify and produce an understanding of public interest(s) through promotion of public debate, engagement with publics and monitoring the effects of relevant technological developments on the interests of potentially marginalised subjects and on social norms**

5.22 Notwithstanding what we have said in this report about the potential moral permissibility of heritable genome editing, it is nevertheless appropriate for the UK to participate in the development of the norms that govern it through action and engagement at an international level. **We endorse the desirability of monitoring and dialogue among nations, which recognises and attends to the diversity of voices within each nation and which may be furthered by support for and participation in a dedicated global observatory or international association and through the work of international institutions**. We find that international institutions have an important role to play in the

negotiation and management of international social, cultural, moral and political differences through transnational and international law and dialogue in the context of technology and knowledge transfer and human mobility.

5.23 One issue in particular where international dialogue is required is to secure the human rights of anyone born following a heritable genome editing intervention. Noting that it is a possible corollary of arguments that linked the enjoyment of human rights to the possession of an unedited human genome, **we conclude that it would be prudent to confirm at the highest level that a human being with an edited genome would be entitled to the full enjoyment of human rights**. One way of pursuing this might be to bring forward an international declaration to this effect, such as a declaration of the United Nations Educational, Cultural and Scientific Organization (UNESCO).[574] We believe genomic technologies, through their distinctive ways of expressing new forms of human identity and difference, carry a particular risk of discrimination. In the UK, protections against genetic discrimination are provided piecemeal in different sectors and generally lack statutory support. The prospect of heritable genome editing interventions gives a particular reason to reconsider the desirability of a legally enforceable, robust and consolidated approach.

5.24 As well as the potential for public funding to promote research necessary to underpin safe, effective and ethically acceptable genome editing interventions, we also acknowledge that much of the development of technologies and translation into practice is carried out using inventions that are subject to patent protection. **We conclude that intellectual property rights in the underlying inventions should be exercised in order to secure the greatest public benefit from genome editing technologies**. One way to achieve this might be for governments and public research and healthcare institutions in the UK and elsewhere to require non-enforcement of relevant patents (and rights in associated software and databases) in the field of human genome editing within the territory of the funding state. To understand the effect of exercising intellectual property rights, it would be desirable for governments, in the UK and elsewhere, to make arrangements for independent monitoring of the impact of any relevant exercise of intellectual property rights on research and public benefit. (This could be carried out in the UK by the independent commission we recommend above.[575]) Furthermore, we believe that consideration should be given to the desirability of securing coordinated group licensing arrangements to facilitate research and innovation (e.g. by UK Research and Innovation and the Department of Health and Social Care the in the UK).

[574] This might be achieved through the amendment of an existing instrument such as the Universal Declaration on the Human Genome and Human Rights.
[575] See Recommendation 7 above.

Recommendations for governments in the UK and elsewhere

Recommendation 8 **We recommend that broad and inclusive societal debate about heritable genome editing interventions should be encouraged and supported without delay**

Recommendation 9 **We recommend, in the light of the potential for new forms of discrimination on grounds of genetic variation, that governments in the UK and elsewhere give fresh consideration to how these risks may be best addressed**

Recommendation 10 **We recommend that governments in the UK and elsewhere should monitor and give consideration to the use of intellectual property rights in order to promote the public interest in having safe, effective and ethical heritable genome editing interventions**

Recommendation 11 **We recommend that governments in the UK and elsewhere should work with international human rights institutions such as the Council of Europe and UNESCO to promote international dialogue and governance with regard to heritable genome editing research and innovation**

Recommendation 12 **We recommend that governments in the UK and elsewhere give consideration to bringing forward an international Declaration affirming that people whose genomes have been edited should be entitled to the full enjoyment of human rights**

5.25 If, as a result of the legislative review we have proposed, heritable genome editing interventions are to be permitted, **we conclude that they should be subject to strict regulation and oversight by a national competent authority**. We make a number of further recommendations about the licensing and regulation of heritable genome editing interventions by the competent authority.

Recommendations regarding licensing and regulation

Recommendation 13 **We recommend that genome editing should be licensed for clinical use only once risks of adverse outcomes have been assessed by a national competent authority (in the UK, the HFEA)**

Recommendation 14 **We recommend that heritable genome editing interventions should initially be licensed on a case-by-case basis**

Recommendation 15 **We recommend that heritable genome editing interventions should be introduced only within the context of well-designed and supervised studies, reporting regularly to a national coordinating authority, and that the effect on individuals and society, including over generations, should be closely monitored as far as possible, compatibly with the privacy of the individuals concerned**

Appendices

Appendix 1: Method of working

Background

The Nuffield Council on Bioethics set up a working party in September 2016 to explore the ethical issues raised by genome editing and human reproduction. The working party met ten times between October 2016 and June 2018. A range of evidence gathering activities were conducted during this period to inform the deliberations of the group.

Call for evidence

The call for evidence took two forms: the first was a 27-question document aimed at professional organisations, stakeholders, and researchers; the second was a broader 16-question online questionnaire hosted by the Survey Monkey website, which sought the views of members of the public with a general interest in genome editing and human reproduction. For further details on the working party's call for evidence, see Appendix 2.

Fact-finding meetings

Three meetings were held with experts in reproductive genetics, genomic research and bioethics.

Meeting with experts in reproductive genetics, 23 March 2017, London

The purpose of the reproductive genetics meeting was to explore recent developments and trends in all areas of reproductive technology and to identify the possible interactions between these technologies and prospective genome editing applications.

- Simon Fishel, Founder and President, Head of Research and Development, CARE Fertility Group
- Tony Gordon, Vice President of Business Development, Cooper Genomics
- Alan Handyside, Principal Scientist, Illumina
- Caroline Ogilvie, Professor of Cytogenetics, King's College London
- Alan Thornhill, Country Manager UK and Senior Scientific Advisor, IGenomix, Associate Director, Market Development, Reproductive and Genetic Health, Illumina
- Dagan Wells, Associate Professor at the University of Oxford and Director at Reprogenetics UK

Meeting with experts in genomics, 31 July 2017, London

The purpose of the genomic research meeting was to explore how developments in genome sequencing and genomics research are likely to interact with prospective genome editing applications and, particularly, which human traits are likely to be amenable to genome editing.

- Maria Cerone, Senior Manager, Cancer Research UK
- Gemma Chandratillake, Course Director, Institute of Continuing Genomic Medicine programme, University of Cambridge
- Myrto Kostadima, Ensembl Regulation Project Leader, Genome Analysis, European Bioinformatics Institute
- Robin Lovell-Badge, Head of the Division of Stem Cell Biology and Developmental Genetics, The Francis Crick Institute
- Zoe McDougall, VP Corporate & Communications, Oxford Nanopore Technologies
- Kathy Niakan, Group Leader investigating the mechanisms of lineage specification in human embryos and human cells, The Francis Crick Institute
- Edward Oakeley, Site Head ASI Genomics, Novartis
- Doug Turnbull, Professor of Neurology, Newcastle University
- Rob Vesse, Software Developer, Cray Inc. (data storage and analytics)

Meeting with experts in bioethics, 31 July 2017, London

The purpose of the meeting on bioethical perspectives was to explore different arguments relating to the moral permissibility of genome editing for a variety of aims.

- Ruth Chadwick, Professor of Bioethics, University of Manchester
- Sarah Chan, Chancellor's Fellow, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh
- Chris Gyngell, Marie Sklodowska-Curie Fellow, Uehiro Centre for Practical Ethics, University of Oxford
- Inmaculada de Melo-Martin, Professor of Medical Ethics, Weill Cornell Medical College
- David Oderberg, Professor of Philosophy, University of Reading
- Danielle Sands, Lecturer in Comparative Literature and Culture, Royal Holloway, University of London
- Robert Song, Professor of Theology, Durham University
- Anthony Wrigley, Senior Lecturer, Centre for Professional Ethics, University of Keele

Two fact-finding meetings held during the first stage of the Council's genome editing work, on 24 February 2016 and 11 November 2015, addressed issues relating to human reproduction, the notes of which were made available to the genome editing and human reproduction working party.

Panel interviews

- David Bentley, Vice President and Chief Scientist of DNA Sequencing, Illumina (10 May 2017, Cambridge)
- Patrick Chinnery, Professor of Neurology and Head of the Department of Clinical Neurosciences, University of Cambridge (10 May 2017, Cambridge)
- John Harris, Lord David Alliance Professor of Bioethics & Director of iSEI, University of Manchester (6 June 2017, London)

- Ted Slater, Global Head, Scientific AI & Analytics at Cray Inc. (5 October 2017, by videoconference)

Research interviews with reproductive and disability rights advocates

A series of six research interviews were conducted between May and August 2017. The purpose of the research interviews was to explore views about the potential social implications of the use of genome editing from a range of perspectives including those of people affected by genetic disease and disability, and reproductive and disability rights advocates.

Interviews were conducted with:

- Teresa Blankmeyer Burke, Associate Professor of Philosophy, Gallaudet University
- Lorraine Cowley, Principal Genetics Counsellor, Institute of Human Genetics, Newcastle University
- Dan Goodley, Chair in Education and Director of Research, University of Sheffield
- Alistair Kent, former CEO of Genetics Alliance UK
- Tom Lichy, Deaf London
- Tom Shakespeare, Professor of Disability Research, University of East Anglia

Evidence reviews

The working party externally commissioned two reviews of literature and evidence.

Dr Rumiana Yotova, lecturer at the University of Cambridge conducted a review of international law, and law and regulation in selected national jurisdictions, relevant to heritable genome editing interventions.[576]

Dr Achim Rosemann, research fellow at the University of Exeter, Professor Xinqing Zhang of Peking Union Medical College and the Chinese Academy of Medical Sciences, Beijing, and Dr Li Jiang, Lecturer at Soochow University, China conducted a review of the legal and regulatory frameworks and provisions relevant to human embryo and human reproductive genome editing research and clinical applications in the People's Republic of China.[577]

[576] Yotova R (2017) *The regulation of genome editing and human reproduction under international law, EU law and comparative law* (background report for Nuffield Council on Bioethics), available at http://nuffieldbioethics.org/project/genome-editing-human-reproduction.

[577] Rosemann A, Jiang L, and Zhang X (2017) *The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China* (background report for the Nuffield Council on Bioethics), available at http://nuffieldbioethics.org/project/genome-editing-human-reproduction.

External review

A draft version of the report was circulated in April 2018 to eleven external reviewers with relevant professional expertise or experience. Reviewers' comments were considered at the working party's meetings in May and June 2018.

The reviewers were:

- Roberto Andorno, Professor of Law, University of Zurich
- Francoise Baylis, Canada Research Chair in Bioethics and Philosophy, Dalhousie University
- Daniel R Brison, Professor and Scientific Director of the Department of Reproductive Medicine, University of Manchester
- Søren Holm, Professor of Bioethics, University of Manchester
- Nils Hoppe, Professor of Ethics and Law in the Life Sciences, University of Hannover and Coram Chambers
- J. Ben Hurlbut, Associate Professor, School of Life Sciences, Arizona State University
- James Lawford Davies, Partner, Hempsons Solicitors, London
- Robin Lovell-Badge, Group Leader and Head of the Division of Stem Cell Biology and Developmental Genetics, The Francis Crick Institute
- Barbara Prainsack, Professor of Sociology, King's College, London
- Sue Price, Consultant in Clinical Genetics, Northampton General Hospital
- Charis Thompson, Professor of Sociology, London School of Economics

Appendix 2: Wider consultation for the Report

Call for evidence

A 'refresh' of the Council's 2015–16 open call for evidence on genome editing was launched on 15 May 2017 and remained open until 14 July 2017. The aim of the refreshed call for evidence was to gather more in-depth information from organisations and individuals with an existing interest in or knowledge about prospective applications of genome editing in human reproduction to inform the working party's examination of the relevant ethical issues. A background document and guide questions were published online. A subset of the individuals and organisations that had replied to the Council's 2015-2016 call for evidence on genome editing were contacted directly and encouraged to update their responses.

The questions posed fell into two categories:

- Perspectives on genome editing
- Biomedical research and human applications

In total, 27 guide questions focussing on uses of genome editing in human reproduction were posed and respondents were encouraged to answer as many as they wished.

Fourteen responses were received; seven from individuals and groups of individuals, and seven from organisations. All the responses were circulated to working party members and considered in detail at the seventh meeting in October 2017. Individual responses are published in full on the Council's website where respondents have given permission for this.[578] The responses received played an important role in shaping the working party's thinking, and the working group is grateful to all those who contributed.

List of respondents to the expert call for evidence

Individuals (7)

- Hille Haker, Chair of Catholic Moral Theology, Loyola University Chicago, USA
- Richard Hayes, PhD, Executive Director *emeritus*, Center for Genetics and Society
- Amarpreet Kaur, Sociology of Reproduction, University of Cambridge
- Jon Olsen, MA Philosophy
- Dr Helen C O'Neill, Lecturer in Reproductive and Molecular Genetics, University College London
- Dr Kenneth Taylor, Dr Ilke Turkmendag, Dr Matthias Wienroth and Dr Simon Woods
- Maggie Zhou, PhD, citizen of USA, former citizen of China and resident of Switzerland

[578] Nuffield Council on Bioethics (2018) *Genome editing and human reproduction: call for evidence responses*, available at: http://nuffieldbioethics.org/project/genome-editing-human-reproduction.

Organisations (7)

- Academy of Medical Sciences (AMS)
- Association of Medical Research Charities (AMRC)
- Marcy Darnovsky, PhD, Executive Director, Center for Genetics and Society
- Ana Nordberg, postdoctoral researcher, Timo Minssen, Professor of Biotechnology Law, Iñigo de Miguel Beriain, PhD, Kirmo Wartiovaara, M.D., Ph.D, Lucia Galvagni, PhD & Oliver Feeney, PhD (COST Action IS1303 – chipme.eu)
- Dr David King, Director of Human Genetics Alert
- Medical Research Council (MRC) and Biotechnology and Biological Sciences Research Council (BBSRC)
- PHG Foundation

Public online questionnaire

The working party launched an online public questionnaire, based on three potential genome editing scenarios. The questionnaire was designed to gather a wide range of responses and a limited amount of qualitative information. It was live for eight weeks between 15 May and 14 July 2017.

In total, 320 people responded to the questionnaire. A summary of questionnaire responses was produced by Nuffield Council staff and will be made available on the Nuffield Council's website.[579] The working party considered the questionnaire responses at its eighth meeting in December 2017. Questionnaire respondents were self-selecting and the results are not intended to be viewed as representative of the views of the population as a whole. The responses received played an important role in shaping the working party's thinking, and the working group is grateful to all those who contributed.

[579] Nuffield Council on Bioethics (2018) *Genome editing and human reproduction: online questionnaire summary*, available at: http://nuffieldbioethics.org/project/genome-editing-human-reproduction.

Appendix 3: The Working Party

Professor Richard Ashcroft

Richard Ashcroft is Professor of Bioethics in the School of Law, Queen Mary University of London. He 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 committees of the Royal College of Obstetricians and Gynaecologists and the Faculty of Public Health, and the ethics of research and public involvement committee of the Medical Research Council. He is also 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 Neva Haites

Neva Haites is Professor of Medical Genetics and Vice Principal for Development at the University of Aberdeen. She is a retired Honorary Consultant Clinical Geneticist at Aberdeen Royal Infirmary. Her recent external roles include being a member of the Human Fertilisation and Embryology Authority and the Committee on Medical Aspects of Radiation in the Environment. She was also Chair of the Biomedical and Therapeutics Research Committee. She has a special interest in inherited predisposition to cancer and chaired the Cancer Genetics Sub-Group of the Scottish Cancer Group for a number of years. As a clinical geneticist she saw individuals and families with a history of cancer and provided counselling, genetic testing and services for surveillance where appropriate.

Professor Joyce Harper

Joyce Harper is Professor of Human Genetics and Embryology at University College London in the Institute for Women's Health where she is head of the Reproductive Health Department, Principal Investigator of the Embryology, IVF and Reproductive Genetics Group, and Director of Education and Director of the Centre for Reproductive Health. She has worked on fertility and reproductive genetics for 30 years, originally working as a clinical embryologist and since 1992 working on preimplantation genetic diagnosis (PGD). She was one of the founders of the European Society of Human Reproduction and Embryology PGD Consortium. Professor Harper is currently working on the social, ethical and legal aspects of fertility treatment, concentrating on social egg freezing and reproductive genetics.

Julian Hitchcock

Julian Hitchcock is a life science partner at Marriott Harrison LLP. In addition to his practice in the law and regulation of medicinal products, medical devices and the processing of biomedical data, he advises leading companies and institutions on legal and regulatory aspects of emerging life science research and technology, particularly in the fields of embryology, cell therapies, genetics and genomics. A former director of the East of England Stem Cell Network, he has been involved in the law of stem cells and regenerative medicine since 2005, and has advised during the legislative phases of significant life science regulations such as the EU In Vitro Diagnostic

Medical Devices Regulation (on behalf of the European Society of Human Genetics). Julian Hitchcock is a member of the Synthetic Biology Leadership Council's governance subcommittee, an honorary lecturer in the School of Bioengineering at UCL, and a former associate of the PHG Foundation and member of the Emerging Science and Bioethics Advisory Committee. He has previously acted as an external reviewer for the Nuffield Council on Bioethics.

Professor Jackie Leach Scully

Jackie Leach Scully is Professor of Social Ethics and Bioethics at Newcastle University. She has a degree in biochemistry and PhD in molecular biology, and held research fellowships in molecular oncology and neurobiology before she joined the University of Basel, Switzerland to help establish its interdisciplinary unit for bioethics. In 2006 she joined the Policy, Ethics and Life Sciences Research Centre (PEALS) at Newcastle University, where she is now Executive Director. Her research interests include disability, genetics/genomics, reproductive technologies, and technologies of identification, mostly using feminist and empirical approaches. She has a particular concern for public engagement and involvement in bioethical discussion, including the voices of traditionally marginalised communities. She is a Fellow of the Academy of Social Sciences, and Editor of the *International Journal of Feminist Approaches to Bioethics* (IJFAB).

Professor Tony Perry

Tony Perry is Professor of Mammalian Molecular Embryology at the University of Bath. His work is centred on the establishment of totipotency in mammals and identified the long-sought principal cytostatic factor. His laboratory continues to study formative processes in early embryogenesis. Professor Perry is interested in developing mammalian genome manipulation and promoting its constructive implementation.

Professor Christine Watson

Christine Watson is 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 genetic approaches including genome editing to study mammary stem cells and the role of individual genes in processes such as cell death and lactation. Professor Watson is also a member of the Nuffield Council on Bioethics.

Professor Karen Yeung (Chair)

Karen Yeung is Interdisciplinary Professorial Fellow of Law, Ethics and Informatics at the University of Birmingham, within the Law School and School of Computer Science. 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 extensively on the use of 'design' as a technique for achieving social and public policy goals, the central theme of her research being their implications for accountability and legitimacy, particularly the way in which they implicate (or fail to implicate) democratic,

constitutional and ethical values. Her most recent and on-going work focuses on the legal, ethical, social and democratic implications of a suite of technologies associated with automation and the 'computational turn', including big data analytics, artificial intelligence, distributed ledger technologies (including blockchain) and robotics. Professor Yeung is also a member of the Nuffield Council on Bioethics.

Glossary

Allele: a particular version of a given gene. Human cells often have two alleles for each gene: one from each parent.

Autonomy: self-government; a person's capacity to make and act on decisions in the course of their life.

Assisted reproductive technology (ART): technologies including *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) used to help couples to conceive. See '*In vitro* fertilisation (IVF)' below.

Base/base pair: the building blocks of deoxyribonucleic acid (DNA) whose order in a genome is synonymous with the DNA sequence of that genome. Human genomes are composed of double-strand DNA containing the four bases: adenine (A), guanine (G), cytosine (C) and thymine (T). The two DNA strands are antiparallel, so that As match up (base pair) with Ts, and Gs with Cs.

Base editing: the direct conversion of a single target DNA base into another (e.g. C to T or G to A) in a programmable manner, without requiring a double-strand DNA cleavage or a donor template.

Cell: the fundamental building block of many biological systems. Humans begin development as a single cell (a one-cell embryo or zygote) that divides and expands to give rise to an estimated 300 or so different cell types in an adult body that typically contains 10^{13}–10^{14} cells.

Characteristic: feature such as eye colour or height that is determined by a complex interaction between genes (or their products), the environment and chance; the relative contribution of each varies for different characteristics.

Chromosome: segments of genomic DNA packaged with proteins and other accessory molecules. Most cells in human adults have 46 chromosomes that together constitute the nuclear genome of each cell.

Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9: a programmable, ribonucleic acid (RNA)-guided, site-specific nuclease. The catalytic protein (Cas9) interacts with a guide RNA (CRISPR or, generally synonymously, gRNA) to carry the Cas9 to the target site in DNA. Cas9 nuclease activity then breaks both strands of the target DNA (to form a double-strand break). Some Cas9 derivatives break only one DNA strand ('nickases'), and Cas9 has also been modified so that it lacks nuclease activity altogether ('dead' Cas9, or dCas9) and can be repurposed by fusing it to other activities (such as histone acetylase) to effect site-directed epigenetic modification.

Deoxyribonucleic acid (DNA): the chemical component of genetic information in mammals such as humans. A DNA molecule consists of a long chain of nucleotides.

Diploid cell: cell containing two complete sets of chromosomes.

Disability: the effect on a person of the conjunction of a physical or mental impairment and the social, political and economic conditions in which they live. There is disagreement over the relative weight of each of these factors in disability.

Embryo: entity during a phase of development immediately following fertilisation up to the formation of a fetus (taken by some to initiate ~11 weeks after fertilisation in humans).

Epigenome: molecular associations with genomic DNA that change its activity, such as how genes are expressed, without altering its nucleotide sequence. Primary examples include covalent modifications to histones such as acetylation and methylation, and to DNA such as methylation, but there are many other epigenetic modifications. On a genome-wide scale, these modifications at any moment define the epigenome. Epigenetic modifications are thought of as being relatively reversible.

Epigenome editing: use of a modified editing enzyme such as 'dead' Cas9 (dCas9) to alter epigenetic marks. This can cause transient or reversible changes to the activity of a gene or genomic region, such as the level at which genes are expressed, without altering its DNA sequence.

Eugenics: projects that attempt deliberately to influence the physical, mental or genetic characteristics of a population, often associated with state coercion.

Gene: the fundamental unit of inheritance. In humans, genes comprise nucleotide (DNA) sequences that each encode a functional product such as a protein or RNA molecule.

Genetic determinism: the view that one or more of a person's behaviour, character and identity are determined by the content of their genome. Also known as biological determinism.

Genetic exceptionalism: the view that genetic information has a special status to which policy and practice should be sensitive and/or that the ethical issues raised by genetic information are different in kind to those raised in other areas of health.

Genome: the full sequence of genetic material (DNA in humans) in an organism or species.

Genome editing: the deliberate alteration of a selected DNA sequence in a living cell.

Genome sequencing: technique for determining the entire sequence of nucleotides in a genome.

Genomics: a discipline in genetics that applies technologies such as genome sequencing methods and bioinformatics to the study of the function and structure of genomes.

Genotype: the genetic make-up of a cell, an organism or an individual, usually with reference to a specific characteristic under consideration.

Germ cells: cells of inheritance: sperm and egg (oocyte). Germ cells (also referred to as gametes) transmit genomes from one generation to the next. During fertilisation, male-derived germ cells (sperm) combine with female-derived germ cells (eggs) to produce a new cell (a one-cell embryo) that is distinct from either, with a unique genome. A 'germ line alteration' is therefore a change made to the genome of a germ cell that would be passed to the next generation and could be passed on to successive generations thereafter.

Germ line: cell lineage (gametes or cells that give rise to gametes) through which the genome of an organism is inherited by each generation from the preceding one.

Heterozygous: having different alleles; that is, the sequence of a given region inherited from one parent differs from the sequence of the corresponding region inherited from the other.

Homology-directed repair (HDR): mechanism by which a double-strand break in DNA is repaired via a different, matching 'template' DNA molecule. For this to occur, the DNA used in repair must contain DNA sequences that perfectly match the sequences (these sequences are said to be 'homologous') on either side of the double-strand break.

Homozygous: possession of identical alleles; that is, identical sequences from each parent for a given genomic region (*cf.* heterozygous).

Induced pluripotent stem (iPS) cell: differentiated cells such as fibroblasts, usually treated by exposure to pluripotency factors such as OCT4, SOX2 and KLF4, such that they give rise to cells resembling embryonic stem cells. Human iPS cells are able to generate many, if not all, cell types found in the body.

***In vitro* fertilisation (IVF):** fertilisation in a clinic or laboratory, as opposed to in the body (*in vivo*). Clinically, IVF refers to a procedure in assisted reproduction wherein eggs are removed from the body (often following artificial stimulation of the ovaries) and mixed with sperm in a dish, or injected with sperm in ICSI. A resulting embryo may then be transferred to a woman's uterus with the intention of establishing a pregnancy.

Mitochondria: essential organelles containing enzymes that convert metabolic products of the cytoplasm into cellular energy. They are present in most human cells (not red blood cells) in many copies.

Mutation: see 'Variation' below.

Non-homologous end joining (NHEJ): cellular mechanism by which a double-strand break in DNA is repaired by joining (ligating) the ends together. During NHEJ, the cell causes a template-independent genomic insertion or deletion ('indel') to be made at or near the site of the double-strand break. Unlike repair via the HDR pathway, the genomic sequence near a repair effected by NHEJ cannot currently be prescribed.

Normative: comprising an evaluative, commendatory or prescriptive component.

Nucleotide: see 'Base' above.

Pleiotropy: influence on multiple phenotypic features of a single gene, such as genes that affect both skin and hair pigmentation.

Preimplantation genetic testing (PGT): genetic testing of embryos created through IVF. Preimplantation genetic testing for monogenic diseases (PGT-M) or preimplantation genetic diagnosis (PGD) aims to diagnose a specific single gene disorders for a couple at known risk. In the UK, the Human Fertilisation and Embryology Authority authorises tests for a list of approved conditions.

Ribonucleic acid (RNA): a polymer of the bases A, C, G and U, where U stands for uracil. It transfers information from genomic DNA to the protein-synthesising machinery of cells.

Social construction of technology (SCOT): the theory that technologies embody social values and choices as fundamental features of their design and form; to be contrasted with the view that technologies are morally neutral and can be separated from the social uses to which they are put.

Stem cell: see 'Induced pluripotent stem (iPS) cell' above.

Technological determinism: the potential of a technology to determine the horizon of possibilities for society in a non-trivial way; that is, that the technologies in use exert a dominant or shaping force on society and social organisation.

Trait: ostensible characteristics or attributes. In the context of 'genetic trait', this means a trait that is correlated with underlying genetic factors.

Transcription activator-like effector nuclease (TALEN): recombinant, site-directed endonuclease. TALENs are proteins (derived from *Xanthomas* sp.) that contain one module synthesised to recognise a specific DNA sequence (e.g. on the genome) fused to a second module (usually the type IIS bacterial restriction enzyme, *Fok*I) that cuts the DNA nearby. TALENs work as dimers, meaning that for each given target cleavage, two TALENs are necessary, each recognising a different adjacent DNA sequence (half-site). TALENs have been used in research, but are being superseded by the CRISPR-Cas9 system, which is generally considered to be easier and quicker to use, cheaper and considerably more efficient.

Transhumanism: an ideology that valorises the transformation of the human condition through the transformation of the human body, such as to promote life extension or cognitive and physical enhancement.

Utilitarianism: the view in moral philosophy that the value of an action or policy is determined by its 'utility' (which may be understood as happiness, welfare, pleasure or some other basic 'good') and that the rightness or wrongness of an action or policy is determined by whether or not it, among all alternative actions or policies, produces the greatest quantity of utility or otherwise.

Variant: sequence of a part of the genome that differs from its counterpart in other genomes, usually genomes that have a commonly encountered sequence at that position.

Whole-exome sequencing (WES): sequencing of the entirety of genomic DNA represented in protein-coding, mature mRNA.

Whole-genome sequencing (WGS): see 'Genome sequencing' above.

'Wild-type' gene: version of a gene found in populations that have not been modified by human beings. 'Wild type' is sometimes used to distinguish a gene or sequence that occurs in nature from a recombinant counterpart.

Zinc finger nuclease (ZFN): hybrid recombinant endonuclease that can be designed to introduce targeted double-strand breaks in DNA. The hybrid comprises one or more (typically three or four) zinc finger motifs derived from mammalian transcription factors tethered to the type IIS bacterial restriction enzyme, *Fok*I. ZFNs work as dimers, so for each given target cleavage, two ZFNs are necessary, each recognising a different adjacent DNA sequence (half-site). This principle applies to TALENs and, like TALENs, ZFNs are being superseded by the CRISPR-Cas9 system, which is generally considered to be easier and quicker to use, cheaper and considerably more efficient.

Zygote: one-cell embryo produced by the union of sperm and egg (the gametes) at fertilisation. Zygotes are totipotent, in that through successive divisions they can engender an entire individual.

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