Genome Editing

Introduction

1 ‘Genome editing’ or ‘gene editing’ is used to describe a number of recently developed technologies that can amend human, non-human animal or plant DNA. The techniques can be applied to both somatic and germ-line cells. Currently, most scientific attention is focused on research, but practical applications, including those aimed at therapeutic human intervention are likely to emerge. A joint statement by the Academy of Medical Sciences, the Association of Medical Research Charities, the Biotechnology and Biological Sciences Research Council, the Medical Research Council and the Wellcome Trust states:

***1a**. Genome editing is a powerful technology that has the potential to improve health. It allows sections of DNA from a genome to be precisely replaced or removed using ‘molecular scissors’. The application of these tools is already having a game-changing effect on research intended to further our understanding of the roles of specific genes and processes in health and disease. In the future, these tools also hold the potential to be applied clinically to prevent or treat lethal and/or seriously debilitating genetic diseases.*

***1b**. The concept of genome editing is not new: for many years, scientists have applied a range of tools to manipulate genetic sequences. However, rapid technological developments in this area – namely the emergence of the CRISPR-Cas9 system – have meant that targeted, highly efficient editing of a genome sequence may become relatively simple. This has cast a spotlight on these technologies, and, in particular, the possibility that they could be applied to enable widespread editing of human cells for therapeutic benefit.*

***1c**, It is important to emphasise that the science is still at a relatively early stage and potential therapeutic applications are not yet here. It is also important to clearly delineate the different ways and contexts in which this technology might be used: clearly distinguishing the use of this technology in a research context compared with its potential application in a clinical setting; as well as distinguishing the use of these technologies using somatic (non-reproductive) or germ (reproductive) cells.*

***1d.** Research using genome editing tools holds the potential to significantly progress our understanding of many key processes in biology, health and disease and for this reason we believe that responsibly conducted research of this type, which is scientifically and ethically rigorous and in line with current legal and regulatory frameworks, should be allowed to proceed. We will continue to support the use of genome editing in preclinical biomedical research as well as studies that progress and refine these technologies. Within the UK, this research may involve the use of somatic (non-reproductive) or germ cells, including human embryos up to 14 days old - within the confines of the HFE Act 2008 - where appropriately justified and supported by rigorous scientific and ethical review.*

***1e**. We believe that genome editing technologies may hold significant potential for clinical application in the future; and we would be open to supporting the development of new therapeutic approaches should the evidence from research advance sufficiently to justify their use. Primarily these advancements have involved the editing of human somatic cells with the aim of repairing or eradicating a mutation that could cause disease or to engineer beneficial changes to allow cell therapy, for example in cancer, where an individual's immune cells might be modified to target cancerous cells.*

***1f**. We also recognise, however, that there may be future potential to apply genome editing in a clinical context using human germ cells or embryos, though this is prohibited by law in the UK and unlikely to be permissible in other European jurisdictions at present. This raises important ethical and regulatory questions, which need to be anticipated and explored in a timely and inclusive manner as the basic research proceeds and prior to any decisions about clinical application.*

***1g**. Active early engagement with a wide range of global stakeholders will therefore be needed, which should include, but not be limited to, biomedical and social scientists, ethicists, healthcare professionals, research funders, regulators, affected patients and their families, and the wider public. Many of these considerations will not be unique to this specific technology, but will apply across a number of future developments in science for the benefit of health.*

***1h**. Frameworks clearly demarcating research use of genome editing from potential clinical use, and carefully distinguishing use of somatic and germ cells, will ensure that the research community remains at the forefront of this novel area, while exploring the complex issues around different clinical applications in a robust and inclusive manner.*

***1j**.The signatories are committed to supporting discussion around genome-editing and its implications. We are progressing this through a number of activities and we will continue to develop and refine our position, informed by the outcomes from such activities.* (September 2015)

2 There is also widespread public interest in human genome editing with encouragement from many to move quickly in this area (as was evident at the Washington International Summit on Human Gene Editing and the London Progress Educational Trust conference on The Science and Ethics of Engineering the Embryo, both held in December 2015). This is understandable, given the potential (though sometimes over-stated) benefits that might accrue from future clinical applications of the technique. As with previous discussions on human fertilisation and embryology such as IVF, embryo research and mitochondrial donation, it is essential that this topic is thoroughly and carefully explored, particularly before any changes in legislation or clinical practice are considered. This has been recognised and accepted by many scientists and bioethicists (see above) and is reflected in the current Nuffield Council on Bioethics consultation on the topic.

3 While there are significant ethical issues associated with both non-human animal and plant genome editing, this paper addresses human genome editing alone and, in particular, germ-line editing as this is the area where the most pressing and distinctive issues are likely to arise. It is important, nonetheless, that human genome editing is not treated in isolation as a totally unique topic, but is set within a wider framework of bioethics. While there are challenges uniquely associated with genome editing, these are not of such a distinctive nature that a general, principled approach to bioethics cannot be applied to this subject. Accordingly, this paper approaches the topic by employing an analytical framework that can be applied to any potential bioethical innovation. Specifically, it examines issues of safety, efficacy, ethics and prudence with the section on ethics focusing on four major ethical principles that help to inform a consistent critique of bioethical issues (see the paper '*Medical Ethics: A Christian Approach*' for a fuller discussion). For a more detailed introduction to the science of genome editing please see the Nuffield Council on Bioethics briefing paper at http://nuffieldbioethics.org/wp-content/uploads/Genome-Editing-Briefing-Paper-Newson-Wrigley.pdf

A Framework for Analysis

Safety

4 This is often viewed as a matter for scientists and clinicians to determine, but issues of safety are far-reaching and require the involvement of others outside research and medical communities. While it is clear that research (and any subsequent clinical applications) ought not to place human participants at notable physical or mental risk, it is less clear where the line is to be drawn for 'notable risk' or who or what might be considered as 'human participants'. It is also important that this discussion includes social as well as physical and mental aspects of safety.

5 Few intrusive clinical procedures, conducted either for research or directly for therapeutic purposes, are entirely risk-free. Procedures necessary for obtaining ova for research or treatment, for example, carry an element of risk to donors, but these are deemed by the HFEA and others to be within acceptable limits. Similarly, the level of risk for IVF procedures is now well documented and closely monitored with participants enabled to give informed consent. Conversely, the necessary benchmarks for mitochondrial donation have not yet been reached. It is essential that margins of risk are clearly established for all participants in genome editing research and clinical application and that no procedures are authorised until it can be demonstrated that they fall within acceptable risk levels. Parliament needs to be assured (within the UK legislative and regulatory framework) that such is the case.

6 In genome editing *research*, the 'participants' (see section on ethics) are early embryos (pre-embryos in some literature). While the use of embryos for research purposes is legal in the UK this does not mean that the practice is unproblematic. The Church of England acknowledges that embryo research aimed at improving therapeutic outcomes for others can be acceptable in some circumstances (though this view is not held by all church members or ethicists), but insists that all human embryos ought to be treated with respect and their distinctive status recognised in keeping with HFEA Code of Practice, Principle 3: *[to] have proper respect for the special status of the embryo when conducting licensed activities*. It is becoming increasingly difficult to discern what 'proper respect' means when large numbers of embryos (particularly in relation to those which have been created purely for research purposes) are used in experiments and then discarded. If human embryos were to become routinely viewed as commodities for experimentation or as a simple means to an ends, this has the potential to have a detrimental effect on the ways in which human life is valued in society. The debate on genome editing presents another significant opportunity for society to review its understanding of the human embryo and to reaffirm ways in which the embryo can be accorded special status and treated with respect.

7 If genome editing were eventually to result in *clinical procedures* being authorised, the need to protect all participants from unacceptable risk is paramount. This must include donors, prospective parents and, primarily, prospective children. The emotional pull to seek to ensure that children are born without debilitating or life-limiting conditions must not outweigh the need to ensure that emerging techniques are used only if the risk of introducing other debilitating conditions to children and their offspring has been effectively precluded.

8 The social risks associated with introducing clinical treatment that might be available only to some prospective parents (particularly if treatment is to become primarily available through

the private sector, as is currently the case with IVF), must not be minimised. The potential for increasing social disparity is a real one that needs to be realistically analysed and satisfactorily addressed prior to any change in clinical practice being introduced.

9 Similarly, the potential impact of genome editing on societal attitudes to disability requires careful consideration. While it would be wrong to suggest that minimising or eradicating some causes of physical impairment ought not to be pursued because of such concerns, the issue deserves to be thoughtfully examined.

10 The borders between treating illness and enhancing human health are porous as are the borders between enhancing health and enhancing human performance/attractiveness. Vaccination, for example does not treat illness, but enhances the human body to resist infection. Similarly, nutrition does not only have an effect on health, but also on physical and mental performance. If genome editing were to become a clinical reality, the implications for human enhancement would need to be fully explored alongside the potential for furthering social disparity noted above. It would be an extremely difficult task to know where to draw the line along the *impairment-enhancement continuum*, but lines would have to be drawn to identify and to avoid unacceptable uses of genome-editing techniques.

11 Attempting to ensure that the offspring of any 'genome-edited' children will not suffer any detrimental effects is a major safety issue. By definition, it is not possible to know how subsequent generations of children might be affected until they exist. Animal experimentation cannot provide a sure guide in all instances. This has the potential to become a significant obstacle in introducing genome editing for clinical purposes unless convincing evidence can be produced that any associated risks have been minimised. Equally, a watertight guarantee would have to be put in place that any emerging problems would halt the continued use of the technique until they are fully resolved.

Efficacy

12 It is essential that, from the outset, each application for research and any subsequent clinical procedures are absolutely clear in what they might realistically achieve. Equally, public discussion of the potential for genome editing to address illness must be measured. Potential clinical applications of genome editing must be explained and discussed in detail rather than promoted with generic claims 'to wipe out' certain medical conditions; a suggestion not supported in researcher literature, but which has been sometimes promoted in the media. (To achieve this aim, every potential parent in the world would have to undergo genetic profiling and every potential mother would have to agree to IVF; clearly an unrealistic prospect.) Prospective parents must not be given false hope and raising expectations which are not likely to be met for many years should be avoided.

13 Genome editing will neither significantly affect the numbers of healthy children to be born nor will it affect the health of existing children; these realities need to be widely understood. Preimplantation Genetic Diagnosis (PGD) already provides a well-tested means by which clinicians may select 'healthy' embryos for IVF implantation while gamete donation from a third party enables potential parents, diagnosed as 'high-risk', to give birth to healthy children. There are, however, circumstances in which PGD is not effective and genome editing could enable some prospective parents to give birth to their genetically related children where a defective gene would otherwise be passed to all of their offspring. The choice that genome

editing can be said to offer is not between a healthy and an unhealthy child being born, but between a healthy child that shares its parents' DNA being born and a healthy child being born that has some of its DNA from a donor. At the same time, it has been argued that genome editing might result in fewer embryos in vitro being discarded as some would be eligible for genetic repair and subsequent implantation.

14 Many medical conditions are polygenetic, caused by an interplay between numbers of genes. Currently, the mechanisms underlying these processes are poorly understood and may not be remedied by current genome editing techniques. Additionally there may be interactions between genes which do not come to light for several generations or which emerge when an altered gene interacts with genetic material introduced by subsequent generations; these can only be observed through longitudinal population studies. At the very least, much greater research into the inter-relatedness of genes is required before the clinical application of genome editing is likely to prove efficacious (or safe) in all but a few cases.

Ethics

15 Issues of safety and efficacy have ethical implications, but there are additional ethical concerns that need to be explored in a discussion of genome editing, before changes in practice or legislation ought to take place.

16 MPA has, in recent years, applied four principled ethical questions to bioethical issues: what course of action might best be seen as life-affirming? Which best cares for vulnerable people? Which best contributes to building a cohesive and caring society? Which best respects individual freedom? The Church has applied these criteria in the priority order listed above.

17 Affirming life requires an examination of the nature and value of human life and the limits that ought to be set for intrusion into both the life process and individual human lives. While it is customary for many to value life in instrumental terms or in terms of the value an individual might set on his or her own life, the Church of England has argued that life ought to be viewed in a wider context and that human life has an intrinsic value apart from its instrumental use or the value set on it by individuals themselves.

18 This means that we ought to view life both as set within the whole environment of human relationships and as part of a continuum from one generation to another. Humans move along a spectrum that begins biologically with human genetic material arising from their parents (gametes) becoming separate, though dependent, human life (zygotes). Individuated human life emerges after the blastocyst stage and eventually individual human persons emerge, although there is no agreement when this final stage is first reached. What value a human life is to be given, cannot be determined by taking a simple 'snapshot' of where that life is on the spectrum at a given moment. Both potential and history ought to be taken into account: a much sought child at the embryonic stage is more than 'a collection of cells' to its parents, just as a much loved relative in end-stage dementia is much more than 'a shell' to his or her family. At the very least, human embryos ought not simply to be seen as routine means towards an end, created purely for the purposes of research; we need to reflect on the ethics of bringing human life into existence in order to experiment on it and then end it. While a positive case can be made for using 'spare' embryos for research: ones that had been originally intended for reproduction but which, for various reasons, could not be implanted, we must take great care

with regard to the impact that genetic editing research might have on the value that we place on human life.

19 Currently, experiments on living foetuses are not permitted, but in order to test the viability and efficacy of genetic changes made to embryos there is a real possibility of pressure mounting to allow some of these to develop to the foetal stage, before licensing the technique for reproductive purposes. The desire by some researchers to extend the moratorium on research beyond the current 14 day limit is a legitimate cause for concern. The present limit recognises the importance of the emergence of the 'primitive streak' heralding the beginning of neural development; regardless of one's views on the status of the embryo and foetus, it is reasonable to argue that as development proceeds along the human life continuum, increasing care ought to be taken with regard to how it is treated. If the beginnings of neural development do not provide a watershed for research, it is difficult to see where else the limit might be placed. At present, there is limited scientific pressure for change and little political will in favour of change, but it would be unwise to assume that the opinions expressed by the House of Lords Select Committee on Stem Cell Research (2002) will remain unchallenged:

19a 'Whilst respecting the deeply held views of those who regard any research involving the destruction of a human embryo as wrong and having weighed the ethical arguments carefully, the Committee is not persuaded, especially in the context of the current law and social attitudes, that all research on early human embryos should be prohibited.

The fourteen days limit

19.b If the respect to be accorded to an embryo increases as it develops, this is a gradual process and it may be difficult to establish precisely the point of transition from one stage to the next. The 1990 Act established 14 days as the limit for research on early embryos. Fourteen days has an objective justification insofar as it represents the stage at which the primitive streak, the precursor of the development of a nervous system, begins to appear. This limit seems to have been widely accepted, and the research done under the Act under licence from the HFEA has attracted very little criticism from those who accept the case for research on early embryos. We have received no evidence to suggest that, if research on human embryos is to continue, there should be a different limit. In point of fact the stage at which stem cells need to be extracted for research is very much earlier than that—at the blastocyst stage—when the early embryo is still smaller than a pinhead. The Committee considers that 14 days should remain the limit for research on early embryos.

What does respect for the early embryo mean in practice?

19.c The Warnock Committee recommended that "the embryo of the human species should be afforded some protection in law" but that protection could be waived in certain specific circumstances.[33] Some of our witnesses took issue with the idea of a status that attracted only limited protection, arguing that it was hypocritical to profess respect for something you were going to destroy. It is true that if an embryo had full human rights it would be inconsistent to do anything that had the effect of destroying it. But to maintain a position that falls short of total protection for the embryo does not in our view equate to a total absence of respect.

19.d Nevertheless there can be confusion about how respect for an embryo should be demonstrated. It may be helpful to try to clarify it. It is sometimes assumed that respect simply means the respectful treatment and disposal of embryonic tissue in the laboratory. This is certainly important, as with any human tissue. The reaction to the removal of organs from children at Alder Hey Hospital shows the importance attached to the physical treatment of human tissue, in that case body parts, even when it is no longer alive.

19.e When living tissue is involved, a further degree of sensitivity is necessary. The 1990 Act requires this to be demonstrated in the following ways:

(a) through the extensive restrictions that are rightly placed on the use of embryos—the 1990 Act permits research on embryos to be carried out only if there is no alternative available and it is necessary or desirable to achieve one of the permitted purposes;

(b) through strict adherence to the rules governing the informed consent of the donors (we return to this issue in Chapter 8);

(c) through restrictions on export where restrictions on use after export could not be overseen or enforced;

(d) through restrictions on mixing with non-human material; and

*(e) through meticulous record-keeping of the creation and disposal of early embryos for research so that every embryo is accounted for'. (*House of Lords Select Committee on Stem Cell Research paragraphs 4.21-4.25*)*

20 To argue that human life has an intrinsic value apart from its instrumental use or the value placed on it by individuals is not, in itself, to determine what that value is, but it is to assert that there is something unique and special in being human. Christian theology grounds this in the concept of the Image of God, but it is not necessary to employ this religious understanding of human life to agree that human life is, in some respects at least, distinctive from other forms of life. That human life has an intrinsic value that ought to be respected, is an innate understanding of many while it underlines much of human rights and criminal law as well as health and social care and can only be abandoned at our peril.

21 Caring for the vulnerable covers a wide variety of interests including prospective donors, parents and children. While it might be contentious to claim that embryos are vulnerable (and if they are, they are not vulnerable in quite the same way as adults or children), the possibility of extending the current 14 day limit for research brings into focus the ethics of deliberately creating, utilising and truncating human life even if these early biological lives are not to be equated with human persons.

22 Caring for the vulnerable must also be reflected in the ways in which those who donate gametes or embryos for research are given full and accessible information with regard to the use to which their donations will be put. It also requires the recipients of any clinical treatment to be made fully aware of associated risks and limitations as well as of the means whereby their treatment became possible through the use of embryo research. For many people this might not present an ethical problem, but for some it will and they ought to be given this information as part of the consent process

23 Paramount, of course, is the welfare of any children (and their offspring) that might be born, following genome editing. This welfare extends to psychological and social aspects of their wellbeing. Tremendous care needs to be taken to ensure that every aspect of their health and wellbeing is explored before any treatment ought to be authorised.

24 Building a cohesive and caring society is close to the heart of every civilised State and many advocates of genome editing view the technique as having the potential to contribute towards achieving this goal. At the same time, it is essential that all aspects of the potential implications of genome editing for society are fully explored. The 'law of unintended consequences' has an inexorable habit of exercising its influence. As previously stated, issues of social disparity, attitudes towards disability and the boundaries between treatment, health and performance enhancement require rigorous examination. Allocation of resources to genome editing over against other techniques that address some of the same issues such as stem cell research needs also to be carefully weighed.

25 Respecting individuals is an important aspect of heath care and is enshrined in the NHS Constitution. For some, however, individual choice has become the over-riding principle that all others serve. While respecting individual autonomy, the exercise of such autonomy must be principled; the context for principled autonomy is set by the affirmation of life, care of the vulnerable and the creation of a cohesive and caring society. Clearly, this places limitations on the freedom of individuals and the amount of resources that ought to be utilized in enabling them to pursue their aspirations within a framework that promotes the common good.

Prudence

26 Even if all safety, efficacy and ethical issues were resolved the question would still remain: is it wise to proceed? Human nature and human societies have a way of producing unexpected outcomes from innocuous or well-intentioned innovations. Measures undertaken for apparently good immediate benefits can, over time, cause a shift in social attitudes which is deleterious and may even undermine the altruism which provided the initial motive for the development. Clinical innovation and changes in legislation, if any, ought to be introduced through the democratic process with ultimate decisions being made by parliament, following widespread, detailed and informed public debate. Human (germ-line) genome editing is, arguably, the bioethical equivalent of splitting the atom; we ought to proceed with very great care to maximise the benefits for society and guard against its misuse.

27. Human somatic genome editing does not present any novel ethical issues (although issues of safety and efficacy remain), but human germ-line genome editing requires a considerably nuanced ethical approach to be taken. Such genome editing *for research purposes* (in keeping with HFEA regulations) whereby a better understanding of human development might be gained, potentially leading to improved treatment of miscarriage-risk or other illness, is welcome (albeit with codicils). Potential *clinical applications* of the technique are more problematic given the number of caveats that have to be addressed, but at present, an amber, rather than a red light, offers continued engagement with the scientific community while being ethically defensible, a position akin to that espoused by the professional bodies' statement quoted at the start of this paper.

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