

Response to the Nuffield Council on Bioethics Call for Evidence on:

## **Genome Editing and Human Reproduction**

### **1: Summary.**

1.1: This document presents some observations that the Working Party may wish to consider in their deliberations on the application of genome editing technologies to human reproduction.

1.2 We suggest that genome editing is significantly distinct from existing approaches to avoiding the transmission of genetic diseases.

1.3 We draw parallels between genome editing and the cell reconstruction and nuclear transfer techniques recently developed to reduce the risk of transmission of some mitochondrial diseases.

1.4 We discuss the desirability of national legislatures, including the UK Parliament, to consider changes to law that would enable genome editing only after regulatory bodies are satisfied as to the safety and efficacy of the proposed techniques.

1.5 We draw attention to the potential distraction from serious consideration of the issues raised by genome editing, by the inclusion of highly speculative and, to us, implausible scenarios in the Public Consultation survey.

### **2: Introduction.**

2.1 We are a group of researchers and social analysts working in the Policy, Ethics and Life Sciences (PEALS) Research Centre and at Newcastle Law School. The views and opinions expressed in this document do not represent institutional positions but are an expression of common views shared by the signatories.

2.2 Our response is informed by work on several research projects, funded by a number of public sector bodies and charities, and that were concerned with rare genetic diseases, assisted reproduction, and new and emerging biological sciences and technologies<sup>1</sup>.

2.3 We welcome the ongoing research to ameliorate the effects of genetic disease and provide safe and effective therapeutic interventions for those individuals and families affected.

2.4 We consider the Council's consultation to be timely, however we are unsure if the design of the public consultation strand will elicit new ideas, information or insights that have not already been identified in previous debates on genetic science and other new and emerging technologies.

2.5 This document addresses a number of issues raised in the consultation and identifies other areas the Working Party and Council may wish to consider.

### **3: The distinctive significance of genome interventions.**

3.1 Intervening in the human genome using gene editing technologies may result in more profound biological and social consequences than those arising from currently licensed techniques in the UK (with the exception of so-called 'mitochondrial donation', see below). Techniques such as genetic screening and PGD result in embryos whose genetic composition has been arrived at within a cellular environment consistent with what might be termed 'natural' reproduction: that is, the nucleus and cytoplasm are linked in a manner that has evolved to enable the correct development of a viable embryo; or prevent the development of a compromised embryo.

3.2 'Mitochondrial donation' techniques such as pronuclear transfer (PNT) enable the construction of an embryo in which the nuclear DNA is different from that which was originally

present in the cellular environment (including the mitochondria) from which the embryo will develop. Concerns about the matching of mitochondrial haplotypes remain, with the HFEA Safety Panel (2016) noting,

The panel maintains its earlier conclusion that consideration should be given to haplotype/haplogroup matching based on the outcome of future research and clinical experience. (HFEA 2016, para 4.20)

This is because the degree of interaction between the mitochondria and the nucleus remains poorly understood (Yamada et al 2016).

3.3 Given the lack of understanding of the interactions between the nucleus and cytoplasm (and its organelles) it cannot be assumed that alterations to the nuclear DNA brought about by genome editing technologies will not alter the interactions between the nucleus and the surrounding cellular environment. In this way, genome editing is distinct from techniques such as genetic screening and PGD.

3.4 The current level of knowledge about heritable traits controlled by multiple genes is low and we consider the premature discussion of such possible interventions as being liable to confuse the arguments. A clear focus on the more likely uses of this new technology in relation to monogenic disease may benefit the quality of the debate. Furthermore, engaging in speculation about enhancement of complex traits (such as intelligence or musical ability) buys into the concepts of genetic essentialism and genetic determinism and implies a very reductive view of what it is to be human.

3.5 We argue that there is an important distinction to be drawn between the editing (altering or cutting out) of deleterious anomalies in the genome (e.g. those that are directly disease causing, the cause of severe impairment or which represent known risk factors) and the insertion of completely new genetic 'information'. This enables a distinction to be drawn between potential therapeutic applications and enhancement applications.

3.6 Even if it becomes feasible to edit in or out certain genes associated with specific diseases or (currently) desirable traits, further research is necessary to understand the complex underlying mechanisms that such editing would have on the body, including the interrelationship that genes have with the environment. A number of scientists involved in genome editing, including Jennifer Doudna, caution that reducing the amount of variation in the gene pool may reduce resilience to newly evolved pathogens<sup>2</sup>. The case studies used in the public survey by the NCoB 'black-box' the lack of knowledge as discussed above, when such considerations and related practices need instead to be opened up to further scrutiny.

3.7 We advise that the Working Party consider that any recommendation they make to proceed with genome editing in the context of human reproduction be highly restricted, at least in the first instance, to life-threatening conditions whose genetic basis is well understood.

#### **4: The obligations of scientists, society and governments.**

4.1 The way in which this science is being represented and presented to public audiences is worthy of further consideration. For comparison: the recent case of IVF-based interventions for mitochondrial disease demonstrates how a coalition of well-meaning clinician-scientists, patient advocates and high-profile public figures (such as Sir Mark Walport and Dame Sally Davies) were able to frame and shape debate in a way that privileged the right of a small group of patients to have a genetically related child over concerns about the wider societal implications of permitting germline-altering treatments<sup>3</sup>. Scientists engaging with genome editing techniques have a duty to represent the limits of their understanding honestly and to engage with critical voices in a constructive manner.

4.2 There was a clear assumption in public debates about ‘mitochondrial donation’ that having genetically-related children was of paramount importance. While accepting that there is a shortage of eggs for fertility treatment and finding suitable children for adoption may not be easy, such difficulties can be overcome. The full range of reproductive options available to people at risk of having children affected by serious genetic diseases must be discussed with them and be highlighted in public discussions of genome editing technologies.

4.3 The NCoB 2016 full report, ‘challenges us to reconsider the reasons for existing prohibitions on deliberately causing genomic alterations that may be inherited by future generations.’ (p113) It is equally valid to ask for a reconsideration of the risks and costs to wider society of permitting a small number of individuals to meet their desire to have a genetically related child. 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). Restrictions in access to publicly funded IVF treatment are not only based on the number of cycles of treatment offered, but also on qualifying conditions; for example neither intending parent should have had a child already. The consideration of the use of gene editing to remove (or reduce) the risk of disease transmission might imply – as is the case with mitochondrial donation – that affected women would have access to public funding for such treatment.

4.4 These observations lead us to advise the Working Party to consider issues of both *distributive justice* and *fairness* in relation to the availability of public funding for all people who require IVF, when considering the implications of introducing genome editing technologies in combination with assisted reproduction.

4.5 The use of genome editing for avoiding certain genetic disorders raises a further concern, *recognition justice*, for those who already live with various genetic disorders. These individuals might feel that they are perceived as less valuable and less desired members of the society. If genome editing techniques are introduced for reproductive purposes, then those who bear the risk of passing a genetic disease to their offspring might feel pressurized to use the techniques to edit the genome of their potential offspring, even though they have safety concerns.

4.6 As noted in the NCoB 2016 full report, we agree that there seem to be no particular additional moral obligations on scientists working on genome editing in comparison to other areas; the need to act morally is already a significant and commonly held responsibility. However, it is clear that some groups or individuals are so positioned that they may have a disproportionate affect by their actions and may therefore have more of an impact than others.

4.7 We agree that the licensing and oversight of genome editing technologies should be no different to existing similar technologies (provided that equivalence of existing technologies with specific genome editing approaches in human reproduction is reliably characterised to be substantial). We are aware that governance of technologies on the basis of substantive equivalence can have pitfalls with wide-ranging negative social and legal impact if the scientific characterisation of the technology is superficial and licensing is left to bodies that follow a commercial prerogative in the process of assigning certification<sup>4</sup>.

4.8 However, the permitting of human genome editing in a manner which renders those changes heritable is a matter of deep significance and importance, both biologically and societally. Such an issue should only be acted upon by UK Parliamentarians after the licensing authority (HFEA) is satisfied as to the safety of the techniques. In that way there is democratic accountability for the decision. In the case of ‘mitochondrial donation’ the UK Parliament permitted the clinical use of the techniques before all the safety experiments had been completed and delegated the final decision on actual use to an unelected arms-length body: the HFEA.

4.9 It should be also noted that any regulations in the UK will have an affect across jurisdictional borders. The effects of permitting genome editing will be felt globally due to the mobility of patients

and scientists. While the NCoB 2016 full report referenced a number of international statements, we suggest additional consultation of

- a) The Declaration of Inuyama (Council for International Organisations of Medical Science),
- b) Convention on Human Rights and Biomedicine 1997,
- c) Universal Declaration on the Human Genome and Human Rights 1997 (UNESCO),
- d) Directive 2001/20/EC of the European Parliament and of the Council,
- e) International Declaration on Human Genetic Data 2003 (UNESCO),
- f) Report of the International Bioethics Committee on the Human Genome and Human Rights (2/10/2015), and
- g) European Group on Ethics in Science and New Technologies: Statement on Gene Editing (11/01/2016).

These international documents and legal instruments underline a number of issues around genetic modification including 'safety of next generations', 'discrimination', 'eugenic practices', 'consent' and 'diversity'. Although these documents were not produced with genome editing in mind, they still provide important debate and guidance on the ethical issues that genetic modification raises, and therefore should be considered as relevant.

## **5: Concerns about the public consultation examples.**

5.1 With regard to the 'public consultation' scenarios, we consider some of these to be implausible (e.g. editing to enhance musical ability or intelligence) and likely to be a sensationalist distraction from the more serious matter of considering the more plausible and perhaps immediate applications of the technology. Such a focus draws attention to the 'designer baby' issue and perhaps offers an easy way of appearing to restrict scientists' ambitions by recommending that such options are not permitted. Examples such as these betray an unwarranted emphasis on genetic determinism and reinforce a reductive view of what makes us human.

5.2 We contend that the consultation documents endorse a 'promissory' outlook and do not address sufficiently the likely challenge of translation from research to therapeutic application; despite such challenges being acknowledged in the full 2016 report. We would draw attention to the similar promissory claims that have been made about other technologies. Expansive predictions were made in relation to gene therapies more than a quarter of a century ago, to personalised (or precision) medicine for over a decade, and to the many variations of human embryonic stem cells and hybrid embryos that have arisen since then; and yet all have hit what we term a 'translational bottleneck'; failing to deliver on the promises made for breakthrough therapies.

## **6: Other observations**

6.1 Scientific practice and deliberation: The drive to be the first in the field to create a child using 'mitochondrial donation' techniques led to a Chinese-American scientist taking advantage of a lack of regulation in Mexico to undertake procedures that are illegal in his home country. In doing so, he and his team showed a wilful disregard for the considerations made by ethics and governance bodies in the US. It seems likely that such drivers will similarly push genome editing of embryos.

6.2 It seems likely that very different national approaches to the regulation and application of genome editing for reproductive health will emerge as countries engage with the regulation of genome editing. This will present national legislators and executives with the need to weigh up opportunities and challenges in developing governance in the context of national debates about

genome editing, international competitiveness in research and in service provision, cross-border reproductive service tourism, and sharing of knowledge and material products across jurisdictions and fields of application. Such considerations could include, developing regulation for application along a continuum of permissive to restrictive; leading on governance efforts whilst other jurisdictions may hold off to study experiences of leaders; defining any intellectual property and patenting aspects for human reproductive genome editing in concert with other governments or unilaterally. At the same time, there are a variety of international regimes (see 4.9 for some examples) that UK legislators may need or want to consider in the process of developing governance for genome editing. These considerations will impact on national governance in the UK, and make it even more significant to consider the wider social and ethical as well as policy and legal aspects of genome editing in human reproduction, both nationally and globally, to inform deliberation and decision-making processes.

6.3 Relatedly, there will be considerable economic interest in both the protection of certain reproductive applications of genome editing processes, their results, and the provision of these and other services. The UK will need to consider if and how to legislate for these nationally and with a view to international and supranational arrangements (e.g. in the EU, USA, the global South), and whether and how it may be desirable and feasible to govern in concert with other jurisdictions. This includes a consideration of what can legitimately be defined as IP and as patent, and which areas of genome editing in human reproduction should be kept free of such arrangements.

6.4 Given the likelihood that legislation will lag behind scientific progress, we might hope that the scientists involved in genome editing, together with social analysts, legal scholars, policy makers, patient interest organisations, and bioethicists, would attempt to develop guidelines for self-governance and ensure that such self-governance is socially responsible, ethically considered, and adhered to. A meeting in the USA in December 2015 may be seen as a start to such a process, and the example of Asilomar in the 1970s has also been raised in the literature; though some scholars have advised against too uncritical an appreciation of the latter process (Jasanoff, Hurlbut and Saha 2015). Ongoing engagement with and development of Responsible Research and Innovation practices in research projects should also be encouraged. We would wish to see the scientists and clinicians involved be as ambitious about the deliberation and governance of genome editing as it is about its scientific programme.

6.5 'Promissory horizons' are being repeated again. The need to obtain funding drives over-claiming, hype, and the concomitant unrealistic expectation generated among potential adopters, and decision-makers. As noted in the NCoB 2016 full report, there is a contract between science and society based on trust, and the continual claims that breakthrough technologies are just about to revolutionise medicine risk impairing that very public trust. What is required is a scientific consensus on avoiding raising overly optimistic and synthetically specific expectations that genome editing could not fulfil. Also required is the public recognition that current understandings of the genome and epigenetics indicate that interactions between genes, and between genes and environment, are highly complex and as yet little charted.

6.6 A generally accepted international consensus on not permitting germline changes was broken by the UK when HM Government permitted the clinical use of mitochondrial 'replacement' techniques. We believe that this will make it difficult for the UK Government to resist calls to legalise genome changes to prevent similar serious diseases. We advise the Working Party to consider the wider international arena and, as Jennifer Doudna (2015) has argued, to develop a 'broader conversation' across jurisdictions and disciplinary boundaries. Opportunities for such engagement need to be created, and the Nuffield Council on Bioethics may be able to provide, or at least work towards such a forum.

We are happy to discuss the above and provide any further information, if required.

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#### **Footnotes:**

1. For example, (i) A socio-ethical investigation of the values and experiences of women volunteering to provide eggs for mitochondrial research under a scheme in which money is offered to egg providers': PI Haines, Wellcome Trust reference WT102609; (ii) An investigation of women's experiences of an IVF egg sharing scheme for somatic cell nuclear transfer research: PI Haines, Medical Research Council reference G0701109.
2. Doudna was quoted in a newspaper article as one of a number of scientists voicing concerns. See New York Times, 17 June 2017, Velasquez-Manoff, available <https://www.nytimes.com/2017/06/17/opinion/sunday/crispr-upside-of-bad-genes.html>
3. For an exploration of these issues see:  
Erica Haines and Ken Taylor. Rendered invisible? The absent presence of egg providers in U.K. debates on the acceptability of research and therapy for mitochondrial disease. *Monash Bioethics Review* (2015) 33:360–378 DOI 10.1007/s40592-015-0046-7  
Erica Haines and Ken Taylor. Sharpening the cutting edge: additional considerations for the UK debates on embryonic interventions for mitochondrial diseases. *Life Sciences, Society and Policy* (2017) 13:1 DOI 10.1186/s40504-016-0046-2
4. For a discussion of such issues in devices governance see:  
Wienroth, McCormack, Joyce (2014) Precaution, governance and the failure of medical implants: the ASR(TM) hip in the UK, *Life Sci Soc Policy* 10: 19.

#### **References**

- Doudna 2015 <http://www.nature.com/news/genome-editing-revolution-my-whirlwind-year-with-crispr-1.19063>
- HFEA (2016) Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update Available [http://www.hfea.gov.uk/docs/Fourth\\_scientific\\_review\\_mitochondria\\_2016.PDF](http://www.hfea.gov.uk/docs/Fourth_scientific_review_mitochondria_2016.PDF) accessed 28/06/17
- Jasanoff, Hurlbut and Saha (2015) CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation, *Issues in Science and Technology*, Volume XXXII Issue 1, Fall 2015, available, <http://www.ask-force.org/web/Genomics/Jasanoff-CRISPR-Democracy-Gene-Editing-2015.pdf>
- Yamada et al., Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes, *Cell Stem Cell* (2016), <http://dx.doi.org/10.1016/j.stem.2016.04.001>

