Transgenerational Genomics
The profession should enhance its role as advocate for the health of the next generation

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No profession should be more involved in the debate about Germline Genome Editing than the members of the Royal College of Obstetricians and Gynaecologists, the Royal College of Midwives, and the practitioners of new reproductive technologies, for the safety of future generations is in their hands. After all, it is our profession which has been the guardian of the health of the next generation and should continue to be so; this can only be achieved by embracing understanding of the new genomic technologies and by becoming involved in the discussions and decisions about their implementation.

The immediate goal should be to encourage an appropriate understanding of modern genomics by all obstetricians and gynaecologists and midwives, by ensuring high calibre genomics teaching in the training curriculum and by incorporating genomics into their professional examinations. It is to this end that the RCOG has established a multidisciplinary Genomics Taskforce (1) to find ways to put genomics high on the professional development agenda. Its aim is to facilitate members' understanding and appreciation of the power of this rapidly advancing field, by direction to existing self-learning modules, and by encouraging the production of new learning opportunities at meetings and courses.

A succession of governments in this country has understood the potential of genomic technology for the practice of medicine; the 2008/9 House of Lords Scientific and Technology Committee report on *Genomic Medicine* and the Independent Cross-Government Advisory Group 2012 report *Building on our Inheritance* predicated the rapid progress of the 100,000 genomes project implemented as a legacy of the 2012 Olympic games. CMO Sally Davies' 2015 insightful report *Generation Genome* (2) outlined the power of genomics to transform medicine in this century and areas of practice in which it could be incorporated. The recent report *Genome UK: a new National Genomics Healthcare Strategy* outlines a 10-year national strategy (3). Key amongst these areas of practice is the complex world of prenatal, preimplantation and postnatal genetic diagnosis.

Genome editing to remove disease-causing mutations is a promising, albeit controversial technology for improving human health; this approach was given an unexpected boost in 2015 by the development of CRISPR, a revolutionary tool that facilitated the ability to correct genetic mutations easily and relatively cheaply. Appropriately its main inventors have been awarded this year's Nobel Chemistry Prize. Although the science of CRISPR has advanced rapidly and associated publications risen exponentially, its use to alter the human genome still holds many concerns about safety and application appropriacy. Indeed, it was Jennifer Doudna, one of the pioneers of this remarkable game-changing technology who called for discussion and restraint in its application; this resulted in the First International

Summit on Gene Editing hosted by National Academy of Sciences in Washington in 2015. However, its report and multiple publications reiterating concerns that the clinical use of germline genome editing was premature did not stop Dr He Jiankui. He shocked the world at the Second Summit in Hong Kong in 2018, reporting that he had edited the genomes of a number of human embryos and transferred them resulting in the births of twin girls whose CCR5 gene had been altered in order to make them less susceptible to HIV (4). Undertaken while the world was deliberating on the most ethical and safe approach to manipulating the embryonic genome (if at all), this event, and the inappropriateness of the gene tackled by Dr Jiankui, spurred the international community into action with two new discussion bodies: the global multidisciplinary WHO Expert Advisory Committee on Human Genome Editing to advise the WHO on national and global oversight and governance mechanisms due to report next year, and the International Commission on the Clinical Use of Human Germline Genome Editing under the banner of the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, and the Royal Society. This latter commission, which reported recently (5) was tasked with bringing together experts to try to thrash out an acceptable way forward (a translational pathway). This added to the two other reports on the same subject from the US National Academies of Sciences, Engineering and Medicine (2017) (6) and the Nuffield Council on Bioethics (2018) (7).

The Royal Society/NAS report which concentrated on heritable human genome editing (which includes germline genome editing) is a cogent reminder that genomics has the power to transform more than just the way we deal with adult human disease, but that alteration of the genome in gametes (and stem cells) has the power to change future generations. Although the UK has clear legislation and regulation through the HFEA, such that editing the nuclear DNA genome in an egg or sperm or embryo is prohibited for the purpose of therapy, Parliament was forward thinking enough to allow one exception - replacement of the mtDNA in an embryo for the sole purpose of avoiding heritable mitochondrial disease not amenable to other technologies such as Preimplantation Genetic Testing (PGT). This legislative permission for a technology that has transgenerational consequences is unique internationally. However, some countries, in the absence of any prohibition in their own territories, have gone ahead with the application of mitochondrial replacement therapy (MRT) (8). Explicit also in the HFEA regulations and the advice given by the expert panel convened to advise the HFEA on the subject (9) is that MRT should be allowed *solely* for the purposes of overcoming genetic mitochondrial disease. Implicit is that it should not be used in the attempt to alleviate infertility by ‘mitochondrial enhancement’ - an unproven technology with little foundation - as mitochondrial transfer is too new and its full ramifications not yet fully understood, albeit that its application for mitochondrial genetic disease may be the least worst option for the family.

Transgenerational genomics is broader than just the science of genome editing, as it involves all aspects of preimplantation and prenatal screening for genetic disease, from preconception counselling to postnatal testing. These aspects of care fall squarely in the domain of the trained obstetrician/gynaecologist, whether fetal medicine specialist, reproductive medicine specialist or generalist, whose participation is essential for its pursuance. Although much discussed by scientists and ethicists (10), the voice of the profession has been relatively silent, despite the fact that germline genome editing cannot be pursued without involvement of the profession, either overtly or silently complicit, as in

the case of He Jiankui, or the pursuance of human reproductive cloning proposed by Severino Antinori and others (11), or the unproven use of MRT for the alleviation of infertility (12).

Our profession has a duty to continue as informed guardians of the health of generations to come and needs to be engaged actively in discussions and decisions about the ethics, timing and extent of implementation of transgenerational genomics.

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References: (all links accessed 29th October 2020)

1. Braude PR. The future is here now. O&G. Winter 2019.
https://www.rcog.org.uk/globalassets/documents/members/membership-news/og-magazine/winter-2019/the-future-is-here-now-winter-2019.pdf

2. Davies SC. Annual Report of the Chief Medical Officer 2016, *Generation Genome* London. Department of Health 2017.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/631043/CMO_annual_report_generation_genome.pdf

3. Brice P. Genome UK: A new National Genomics Healthcare Strategy. PHG Foundation Blog 22 Sept 2020.
https://www.phgfoundation.org/blog/new-national-genomics-healthcare-strategy

4. Cyranoski D. The CRISPR-baby scandal: what's next for human gene-editing. Nature. 2019; 566 (7745): 440-442.
https://www.nature.com/articles/d41586-019-00673-1

5. Heritable Human Genome Editing. Report of the International Commission on the Clinical Use of Human Germline Genome Editing. National Academies of Sciences Engineering and Medicine and the Royal Society 2020. Washington DC. National Academies Press.
https://www.nationalacademies.org/our-work/international-commission-on-the-clinical-use-of-human-germline-genome-editing

6. Human Genome Editing: Science, Ethics, and Governance. National Academies of Sciences, Engineering, and Medicine. 2017 Washington, DC: The National Academies Press..
https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

7. Genome Editing and Human Reproduction: social and ethical issues 2018. Nuffield Council on Bioethics London.
https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction

8. World's first baby born with new "3-parent" technique. New Scientist. 27th Sept 2016.
https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/

9. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease though assisted conception: 2016 update. HFEA 2016.
https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf

10. Adashi EY and Cohen IG. What would responsible remedial human germline editing look like? Nat. Biotechnol. 2020; 38:398–400.
https://www.nature.com/articles/s41587-020-0482-7

11. Abbott A. Disbelief greets claim for creation of first human clone. Nature. 2002;416, 570.
https://www.nature.com/articles/416570a

12. Heffner C. First baby born in mitochondrial donation for infertility trial. Bionews. 2019;995.
https://www.bionews.org.uk/page_141058