1 Clinical and Scientific Background

The articles in this special issue explore a host of complex issues raised by the emergence of novel mitochondrial replacement techniques (MRTs) to reduce the risk of transmitting mitochondrial disease to future persons.

Mitochondrial diseases are among the most common neuromuscular diseases and serious mitochondrial diseases may cause suffering and premature death.\(^1\) Mitochondria are the intracellular structures that produce energy for cell functions and each mitochondrion has a maternally inherited genome (mtDNA) that is separate from the cell’s nuclear genome (nDNA). One way that mitochondrial diseases arise is when harmful mutations occur in mtDNA and this mutant mtDNA is present in harmful concentrations in the body. In such instances, mitochondria are unable to provide the energy that cells need in order adequately to perform bodily functions. Since the mitochondrial genome is maternally inherited, so too are mtDNA diseases. Some examples of mtDNA diseases include LHON (Leber hereditary optic neuropathy) and NARP (neurogenic muscle weakness, ataxia,
retinitis pigmentosa). As names such as ‘NARP’ suggest, mitochondrial diseases often present as a diverse collection of symptoms. There are no known cures for mtDNA diseases. Women carrying harmful mtDNA mutations often face uncertainty surrounding whether or not their genetic children will inherit a serious mitochondrial disease. Much of this uncertainty depends on the type of mtDNA mutation an intending mother is carrying: a homoplasmic mutation or a heteroplasmic mutation. If harmful mutations are found in all of the mtDNA in the body this is known as homoplasmy. Women with serious homoplasmic mtDNA diseases will always create children who are homoplasmic disease carriers. In contrast, the presence of harmful mutations in some but not all mtDNA in the body is known as heteroplasmy and the transmission of heteroplasmic mtDNA diseases across generations is less predictable. As a consequence, there is often clinical uncertainty surrounding whether embryos carrying heteroplasmic mtDNA mutations will develop into persons with serious mitochondrial disease. Due to this predictive uncertainty, existing tests such as pre-implantation genetic diagnosis (PGD) are often unable to help intending mothers determine whether a serious mtDNA disease will manifest in any offspring they create. Therefore, intending mothers with mtDNA diseases have historically had two reproductive choices: either abstain from having genetic children (e.g. forgo having children, adopt a child, or use an egg donor with in vitro fertilisation (IVF)) or have a genetically related child with the risk that the child will have a serious mitochondrial disease.

5 However, if the mother is a homoplasmic carrier the risk will be 100% that the child will also be a carrier.
The emergence of MRTs offers hope to intending mothers who want to have genetically related children free from serious mitochondrial disease. Two novel interventions have been developed to reduce the risk of mtDNA disease transmission: maternal spindle transfer (MST) and pronuclear transfer (PNT). Maternal spindle transfer involves removing the nDNA from an intending mother’s egg with unhealthy mitochondria and inserting that nDNA into an enucleated\textsuperscript{6} donor egg with healthy mitochondria.\textsuperscript{7} The egg carrying the healthy mitochondria (and mtDNA) from the donor and the nDNA of the intending mother can then be fertilised to create a healthy embryo (see Figure 1: Maternal Spindle Transfer).

\textbf{[Insert Figure 1]}\textsuperscript{8}

In contrast, PNT involves fertilising an intending mother’s egg (carrying unhealthy mitochondria) and a donor’s egg (carrying healthy mitochondria) to create two embryos. The nDNA from the embryo with healthy mitochondria is removed and discarded. Next, the nDNA from the intending mother’s embryo (with unhealthy mitochondria) is transferred into the enucleated embryo carrying healthy mitochondria. The result is an embryo carrying healthy mitochondria from the egg donor and the nDNA contributions from the intending mother and the genetic father (see Figure 2: Pronuclear Transfer). It is estimated that both MST and PNT could become available for clinical use in the near future.

\textbf{[Insert Figure 2]}\textsuperscript{9}

\textbf{2 Law, Regulation and Policy}

\textsuperscript{6} ‘Enucleated’ refers to the fact that the nDNA has been removed from the egg or embryo.

\textsuperscript{7} ‘Healthy mitochondria’ refers to mitochondria without harmful mtDNA mutations and ‘unhealthy mitochondria’ refers to mitochondria with harmful mtDNA mutations.

\textsuperscript{8} Image used under licence from Rebecca J Kent www.rebeccajkent.com

\textsuperscript{9} Image used under licence from Rebecca J Kent www.rebeccajkent.com
Given the novelty of these techniques, the question of whether and, if so, how they should be legalised is a large and important one. For the United Kingdom (UK), the first country to legalise these techniques, this question arose in the context of its long-established statutory framework, originating in the Human Fertilisation and Embryology (HFE) Act 1990, governing assisted reproductive techniques such as IVF and embryo research. When the Act was amended in various ways in 2008, in the light of progress in research relating to MRTs a section allowed for the possibility of regulations subsequently being passed to permit the use of MRTs in treatment.\(^\text{10}\) After this, in 2012, the UK Government asked the statutory regulator, the Human Fertilisation and Embryology Authority (HFEA), to seek public views on MRTs. Based on a 2013 Report of the evidence it collected, the HFEA recommended to the Government that it proceed with the envisaged regulations,\(^\text{11}\) in relation to which there was in turn a further process of public consultation.\(^\text{12}\) Finally, following Parliamentary debate, the regulations were subsequently passed in Spring 2015 and came into force that Autumn though, at the time of writing, MRTs have not yet entered clinical practice.\(^\text{13}\)

Before and during the Parliamentary debate, various ethical and legal issues were discussed. One of the most significant concerned the widespread international prohibition of germline genetic modification and the various international statements and conventions which restrict or prohibit these. In this light, how was the proposed UK legal move to be viewed?

\(^\text{10}\) HFE Act 1990, as amended by the HFE Act 2008, s. 3ZA(5). It should be noted that, under both the original and the amended HFE Act, licenses can only be granted for research, treatment or storage of genetic material: s. 11.

\(^\text{11}\) This process is described in: Human Fertilisation and Embryology Authority (HFEA). 2013. *Mitochondria Replacement Consultation: Advice to Government.* London, UK: HFEA.


\(^\text{13}\) The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015; in force 29 October 2015.
Of particular note is the Council of Europe’s 1997 Convention on Human Rights and Biomedicine, a legally binding convention signed by most European states though not, as it happens, the UK. Article 13 states that ‘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’. Various questions arise regarding how this should be interpreted. Although not a signatory, the UK Government sought to define MRTs in such a way that they are outside the category of ‘germline genetic modification’. This was done by taking the view that it is the nuclear genome that is really at stake in this concept since it is that genome, along with environmental factors, that is responsible for “shap[ing] our personal characteristics and traits”. For any signatory state wishing to legalise MRTs, the UK strategy of holding that MRTs do not involve germline genetic modification would be one way forward.

In contrast to the approach of the UK Government, in early 2016 a US Food and Drug Administration (FDA) commissioned report of an ad hoc committee of the US Institute of Medicine (IOM) held that MRTs would be a form of ‘germline genetic modification’, at least if female offspring are born. It also rejected the notion that MRTs can be understood

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14 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, ETS No. 164, Oviedo, 4 April 1997; 35 Member State signatories, with 29 ratifications, at 22 September 2016.

15 UK Department of Health, above n. 12, p. 15.

16 UK Department of Health, above n. 1, para. 1.5. The original HFE Act prohibited, in Sched. 2, para. 3(4), ‘altering the genetic structure of any cell while it forms part of an embryo’. This was interpreted by an HFEA License Appeal Committee, with scientific and lay opinion in support, to refer to the nuclear genome, in order to permit research into PNT in Newcastle in 2005: HFEA. Mitochondrial DNA Disorders – Is There a Way to Prevent Transmission? Summary of How the HFEA Made its Decision to License this Project of Research. 2005. RO153, paras 14-18. See now HFE Act 1990 (as amended), Sched. 2, para. 1(4), which states (in part) that ‘[a] licence under this paragraph cannot authorise altering the nuclear or mitochondrial DNA of a cell while it forms part of an embryo, except for the purpose of creating something that will by virtue of regulations under section 3ZA(5) be a permitted embryo.’ Our emphasis.

17 On 16 March 2016, the Institute of Medicine was renamed the ‘Health and Medicine Division’ or ‘HMD’.

18 Institute of Medicine, above n. 2, p. 6.
as ‘treatment’, other than in relation to prospective parents,\(^{19}\) thus perhaps implicitly questioning those aspects of the UK policy and regulatory debate that cast MRTs as such in relation to future people.\(^{20}\) However, in line with the UK Government, the Report likewise emphasises the greater significance of the nuclear, as compared with the mitochondrial, genome as regards ‘physical and behavioral characteristics’.\(^{21}\) Overall, the Report recommends a cautiously permissive approach to the potential regulation of MRTs.\(^{22}\)

Questions regarding the purpose of MRTs, including whether or not they ‘treat’, as well as how they should be understood in relation to the concept of germline genetic modification, are likely to be prominent in future debates elsewhere, in addition to questions such as the status of the mitochondrial donor, and whether people created by MRTs should be able to establish the identity of the donor. Despite now having a system of open-identity donation for traditional gamete donation, the UK has rejected this for MRTs, essentially on the basis of the nature of the mitochondrial donor’s contribution, relating to the mitochondrial rather than the nuclear genome.\(^{23}\)

### 3 The Papers

Turning now to the contents of this volume, the six papers selected are tremendously diverse and yet there are core concerns that many of the authors share. These include: an


\(^{20}\) See e.g. UK Department of Health, above n. 1, p. 5; but note also our comment regarding the scope of possible purposes for licenses under the HFE Act (as amended), above n. 12.

\(^{21}\) Institute of Medicine, above n. 2, p. 107.

\(^{22}\) *Ibid.* p. 7. But note that the Report recommended (contrary to the UK position) that MRTs should only be used to create male offspring, until sufficient post-birth information regarding the safety of the techniques has been collected, however long this may take, p. 13.

interest in effects on ‘identity’ and the many different senses of that term; the question alluded to earlier of what counts as therapy and whether it matters ethically whether MRTs are therapy (and, if so, what kind of therapy); and questions of language and communication, ranging from arcane classificatory and conceptual questions right through to more practical ones about media depictions of science.

Françoise Baylis’s paper engages with questions which are fundamental not only to mitochondrial replacement but to the whole future of human reproduction. She challenges the frequently made claim that ethics ‘lags behind’ science. Such claims are often flawed both empirically and conceptually: conceptually because the very idea that ethics and science should proceed along parallel tracks in a temporally aligned way is questionable; empirically because bioethicists do routinely produce work on future scientific possibilities (such as human reproductive cloning and ectogenesis).24 Her paper also tackles fundamental questions about what value we should attach to genetic relatedness, about whether having one’s own genetically related child is a need or merely a want, about how we should allocate inevitably limited human and financial resources, and whether expensive reproductive technologies (such as MRTs) are a defensible use of these.

As noted already, the idea of ‘identity’ figures prominently and is explored, in three very different ways, by Matthew Liao, César Palacios-González, and Jackie Leach Scully.

Liao is interested in whether MRTs merely alter the characteristics (‘qualitative identity’) of a determinate future child or whether they instead lead to the creation of a completely

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different, ‘numerically distinct’, child. He argues that MRTs alter numerical identity and that this has ethical implications. If MRTs merely altered the characteristics of a determinate future person, then that individual could later claim they had been harmed or benefitted by the techniques. But this is not possible, Liao suggests, if MRTs affect numerical identity for, without MRT, the person making the claim would not have existed at all.

This issue, along with the related one of whether MRT should be thought of as therapy or instead as selective reproduction, is also discussed by César Palacios-González, in a paper exploring what ‘bioconservatives’ – particularly those working within the theoretical framework of Jürgen Habermas – should think about MRT. One necessary condition for the permissibility of prenatal genetic interventions posited by the Habermasian framework is that they should be therapeutic. For this reason, Palacios-González suggests that Habermasians ought perhaps to view PNT and MST using preselected gametes more favourably than MST without preselected gametes. For whereas the former are arguably therapeutic, the latter looks more like an instance of selective reproduction because the numerical identity of the resultant person is altered.

Palacios-González’s main conclusion is that bio-conservatives should view MST using preselected gametes, but no other form of MRT (including PNT), as morally acceptable. For while PNT can also meet the therapy-criterion, it is inconsistent with Habermas’s beliefs about the value and use of human embryos; this however is not a problem for MST since it acts on gametes rather than embryos. This conclusion is interesting for it implies that even

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‘bioconservatives’ need not advocate a blanket ban on MRT and that they should instead take a nuanced view in which (what he terms) ‘MSTpg’ (MST with preselected gametes) is the only permitted form.27

Exploring a different sense of ‘identity’, Scully asks how MRTs might influence the sense of self of the person created and how narrative identity might be affected. She avoids jumping to pessimistic conclusions, but does raise several potential challenges for MRT-children. One is that, as a new and unusual social group, they may simply lack a clear origin-narrative. Another is that their sense of self may be adversely affected by media coverage, such as ‘three parent IVF’ discourse and the implication that MRTs produce ‘healthy but unnatural embryos’.28 As a practical response, Scully suggests systematic monitoring of how MRT-children and their families are talked about and that efforts may need to be made to ‘counter potentially hurtful, harmful or limiting identity stories with more nuanced ones based on accurate empirical knowledge’.29 On a more general level, she suggests that effects on narrative identity perhaps deserve more attention than they often get in bioethics and policy discussions.

Like Scully, Cathy Herbrand is concerned with media representations. In her paper, she sets out to compare and contrast two different areas of discourse. The first is the recent UK parliamentary and public debates about ‘legalisation’. These, she argues, often presented MRTs as a ‘straightforward and unique solution’, with the families affected seen as ‘a

homogenous group ... characterised by desperation’. 30 The second is an ongoing study of families affected by mitochondrial disease. Herbrand suggests that there is a gap between media portrayals of MRTs ‘as a kind of “miracle solution”’ and the perspectives of these families.31 The families are more diverse than is sometimes assumed, with each one ‘facing specific issues in terms of quality of life’, and fewer families standing to benefit than the media and public discourse suggests. 32

Finally, the issue of whether MRT is therapy – and, if so what kind - is tackled by Ainsley Newson and Anthony Wrigley. One important question for them is how MRT relates to the standard distinction between somatic and germline gene therapy. Exploring this issue raises not only the question of whether MRTs are ‘somatic’ or ‘germline’ but also the question of whether it should be thought of as ‘gene therapy’ at all. Reasons for at least questioning this include the fact that MRT involves replacing whole extra-nuclear organelles as opposed to targeting individual genes and (as discussed earlier in relation to Liao and Palacios-González) the fact that some types of MRT may be more like selection than therapy.

In response to various challenges for the established classificatory framework, Newson and Wrigley propose a new category into which MRT should fall: a subclass of genetic modification which they term ‘conditionally inheritable genomic modification’ (CIGM). MRTs are ‘conditionally inheritable’, rather than being straightforwardly ‘germline’ or ‘somatic’ because of factors such as ‘matrilineal inheritance, bottleneck effects and unpredictability in

30 C. Herbrand. Mitochondrial replacement techniques: who are the potential users and will they benefit? Bioethics 2016; 31.1: [insert page numbers].
31 C. Herbrand. Mitochondrial replacement techniques: who are the potential users and will they benefit? Bioethics 2016; 31.1: [insert page numbers].
32 C. Herbrand. Mitochondrial replacement techniques: who are the potential users and will they benefit? Bioethics 2016; 31.1: [insert page numbers].
mitochondrial segregation’. This novel classification of MRTs has some ethical implications: for example, if correct, it shows that their ‘automatic prohibition as germline therapies is not warranted’. Newson and Wrigley rightly make clear however that many of the ethical and policy issues here don’t depend (or don’t depend wholly) on classification. And so dealing with these classificatory issues, whilst helpful and valuable in many ways, will not settle all of our ethical questions.

MRTs raise an extraordinarily wide range of ethical issues, many of which have application much more broadly across the fields of genetics and human reproduction. Hence we do not claim that these papers cover the entire set of issues raised, nor that they are representative, and clearly there is plenty of scope for further work on this topic: ranging from practical policy questions about mitochondrial donor anonymity and public funding of MRTs, through to conceptual issues about identity and the distinction between gene therapy and selective reproduction. Nonetheless, we do feel that these six papers take us forward in substantial and interesting ways and would like to thank our authors for their contributions, as well as everyone else involved in the process: including the many people who agreed to act as referees for this special issue and everyone who attended our symposium on the Ethics of Mitochondrial Replacement at King’s College London in September 2015.

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