In 2015, the UK became the first country to approve the use of mitochondrial donation. This novel in vitro fertilisation treatment was developed to prevent transmission of mitochondrial DNA (mtDNA) disease and ultimately give more reproductive choice to women at risk of having severely affected offspring. The policy change was a major advance that surmounted many scientific, legislative and clinical challenges. Further challenges have since been addressed and there is now an NHS clinical service available to families with pathogenic mtDNA mutations that provides reproductive advice and options, and a research study to look at the outcome at 18 months of children born after mitochondrial donation.
Scien\textbf{tific challenges}

Mitochondrial donation can be performed between unfertilised oocytes at the metaphase II stage (MST) or fertilised zygotes at the pronuclear stage (PNT) [6–8]. Both techniques were initially developed in animal models, with pronuclear transfer in mouse embryos being pioneered by McGrath and Solter in 1983 [9]. Proof of principle studies using abnormally fertilised human embryos were essential to optimise the PNT procedure but could only be performed once a license had been approved by the Human Fertilisation and Embryology Authority (HFEA) (the statutory regulator of all IVF procedures and embryo research in the UK). Once these research studies had established that PNT was a feasible option to prevent transmission of mtDNA diseases [7], preclinical studies to evaluate the safety and efficacy of the technique were crucial and relied on the use of normally fertilised human embryos [10]. The availability of these embryos for research was another significant
challenge but was overcome by the introduction of an ‘egg sharing’ scheme for those going through IVF treatments and the willingness of altruistic egg donors living in the North-East of England. The studies that followed were evaluated in detail by an independent scientific panel of experts on four separate occasions. In 2016, the final review by the scientific panel concluded that ‘it is appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients’

Policy challenges
In the UK, all IVF procedures are regulated by the HFE Act which, before the recent amendment, did not permit the implantation of an embryo in a woman after PNT or MST. Thus, once the science was making significant progress, it was also important to consult widely to try and change the legislation to allow the clinical application of mitochondrial donation. This required widespread public consultation and ethical debate. At the centre of this public dialogue were mitochondrial patients, their families and patient organisations who were pivotal to the policy change. This involved patients and families sharing their experiences of mitochondrial disease with both the policy makers and the media to ensure that the patient voice was heard throughout the extensive consultation.

Another important challenge involved engaging patients, the public and policy makers with the complex science behind mitochondrial donation. This was made somewhat harder by the overused media term ‘three-parent baby’ that was often misinterpreted and, in our experience, led to considerable misunderstanding of the technique. Many different organisations supported this and it allowed people to form their own views based on a greater understanding of the issues.

Clinical challenges
For mitochondrial donation to be made available, the HFEA set very specific criteria. The IVF clinic needs a licence to conduct research and treat patients, which requires a detailed assessment of a clinic’s suitability, looking at existing staff expertise, skill and experience in either MST or PNT. A licence was granted to the Newcastle clinic in 2017. Another important consideration is the development of a clinical service that provides couples with specialist advice about their reproductive options, supports them through the mitochondrial donation procedure and allows for the long term follow-up of children born. A care pathway has been developed in Newcastle following extensive consultation with mitochondrial disease patients and their families [4].

It is important that women who carry pathogenic mtDNA mutations are informed of their reproductive options as early as possible so as not to limit the choices available to them. For those who select an IVF-based option, it is important to inform couples that, as with any IVF treatment, the procedure does not guarantee a pregnancy and may fail at any stage. Furthermore, predicting the success of mitochondrial donation in terms of achieving a baby is challenging given the limited clinical experience and couples must be made aware of this and counselled appropriately. For those wishing to proceed with mitochondrial donation, each individual treatment needs to be approved by the HFEA. There remain some challenges in identifying which women could benefit. This is particularly true for patients with heteroplasmic mtDNA mutations where other techniques such as PGD may be an alternative. The HFEA regulations stipulate that mitochondrial donation may only be considered when PGD is unlikely to succeed but there are challenges in predicting which women this will apply to. For more common mtDNA mutations, information from large cohorts have allowed a prediction tool to be developed [11] but for rarer mutations this remains a challenge and obtaining detailed genetic information from the family is crucial. Another pressing issue is the availability of women who would consider donating their eggs for the mitochondrial donation procedure. There are strict criteria that must be met by any potential egg donor, including age, health status and where they live in relation to the fertility centre, which is in addition to the commitment required by anyone who volunteers to go through the egg donation process.

Conclusion
Mitochondrial donation is offering new hope to families who carry pathogenic mtDNA mutations and has met considerable scientific, legislative and clinical challenges. It highlights the importance of including patients in all aspects of medical research and demonstrates that many of these challenges can be overcome with their support.
Mitochondrial donation is a new IVF technique that enables women who carry mtDNA mutations to have their own biological children.

Changes in the law were required to enable mitochondrial donation to proceed in UK.

Women in the UK with pathogenic mtDNA mutations are able to access a specific NHS service which provides comprehensive advice and a variety of reproductive options to enable them to have healthy offspring with low risk of mtDNA disease.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Funding
This work was funded by the Wellcome Centre for Mitochondrial Research (203105/Z/16/Z); MRC Centre for Ageing and Vitality (MR/L016354/1); MRC Centre for Translational Research in Neuromuscular Disease Mitochondrial Disease Patient Cohort (G0800674); the UK NIHR Biomedical Research Centre in Age and Age Related Diseases award to the Newcastle upon Tyne Hospitals NHS Foundation Trust; The Lily Foundation; and the UK NHS Specialist Commissioners ‘Rare Mitochondrial Disorders of Adults and Children’ Service.

Author Contribution
L.C. and D.M.T. wrote the manuscript. J.L.M. led on all patient engagement aspects of the project. All authors reviewed the final manuscript.

Acknowledgements
We would like to thank the patients and patient organisations for their involvement in all aspects of this work.

Abbreviations
HFEA, Human Fertilisation and Embryology Authority; IVF, in vitro fertilisation; MRT, mitochondrial replacement therapy; MST, maternal spindle transfer; mtDNA, mitochondrial DNA; PNT, pronuclear transfer.

References