
Summary

1. In April 2011, we wrote to the Secretary of State for Health, together with partner organisations, calling for the introduction of regulations to enable new techniques that aim to prevent the hereditary transmission of mitochondrial disease caused by mutations in mitochondrial DNA (mtDNA) to be used in clinical practice, if sufficient pre-clinical evidence is obtained.¹ We welcome the scientific progress that has been made since then and the thorough approach that has been taken to ensure that the full range of views and evidence are taken into account with regards to these new techniques. **The Academy is in full support of introducing regulations to enable these techniques to be used to prevent the transmission of serious mitochondrial disease, providing that further research continues to demonstrate their safety and efficacy.** We would advocate that Parliament amend the Human Fertilisation and Embryology Act 1990 (as amended), to enable the use of these new techniques in the clinic.
2. We do not think that the two approaches to the prevention of mitochondrial disease, pronuclear transfer (PNT) and maternal spindle transfer (MST), should be differentiated between at this point. As long as future research does not rule out the application of either PNT or MST on the grounds of safety or feasibility, we consider that the development of both techniques should proceed to allow for their viability as potential clinical treatments to be assessed.
3. We understand that the Department of Health (DH) intends to ask the Human Fertilisation & Embryology Authority (HFEA) to update the 2011 scientific review on the safety and efficacy of the techniques based on the latest evidence to sit alongside the HFEA report on the public consultation. We welcome this and would strongly urge that this should include detailed consideration of whether non-human primate (NHP) research should remain a prerequisite for the introduction of the techniques in humans, as specified by the original HFEA scientific review.
4. There are substantive difficulties in assessing the likelihood that mitochondrial disorders may arise in offspring and the subsequent severity of the disease. As such, we would not recommend that the HFEA (or whichever regulatory body oversees the treatment licences) should require every couple requesting PNT or MST to be individually assessed by the HFEA to determine if their risk is 'serious'. Rather, we would support patients being allowed to decide whether or not to receive mitochondria replacement treatment (and if so, which technique is preferred) in liaison with their clinicians, subject to all safety and efficacy requirements being met. However, to ensure that the procedures are not carried out for spurious reasons that might put a resulting child at risk, we consider that it would be preferable for potential patients to be referred by experts in

¹ The Academy of Medical Sciences (2011). *Treatments to avoid transmission of mitochondrial disease*. <http://www.acmedsci.ac.uk/p47prid100.html>.

mitochondrial disease, and that the HFEA should maintain a list of approved referrers.

5. Furthermore, we have previously highlighted the need for closer oversight of the introduction of new assisted reproduction technologies (ARTs). Given the novel nature of these procedures, we feel that it should be a condition of licensing for these techniques that the clinic is required to regularly report data on safety and efficacy of treatments to the HFEA. Further, due to the imperative for evaluation of the impact of these techniques in the long-term, we would strongly recommend that a process is undertaken to identify the optimal methods for ensuring follow-up takes place and define the standards that are to be met. Treatment licences for these techniques should then only be granted to clinics that have documented plans for the long-term follow-up of offspring in place, which meet these standards. Assessing the implementation of this plan should be part of the inspection process carried out by the HFEA. There should be appropriate oversight of the HFEA to ensure that appropriate follow-up of efficacy and safety is being carried out.
6. Our elected Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service, some of whom have contributed to this response and who would be happy to provide further evidence if required. In addition, the Academy hosted an informal public engagement event on the topic of mitochondria replacement in partnership with Science London, a volunteer organisation linked to the British Science Association, in November 2012. The participants highlighted some key issues, which have been taken into consideration below.

Introduction

7. The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. In January 2012, the Academy welcomed the announcement by the Wellcome Trust that it had established a new Centre for Mitochondrial Research at Newcastle University to undertake research to understand, and potentially prevent, inherited mitochondrial diseases.² We also welcomed the announcement that the Secretaries of State for Health, and for Business, Innovation and Skills had asked the HFEA and Sciencewise-ERC to undertake a public consultation to seek the views of the public and patients in order to take these into account alongside scientific evidence and expert ethical opinion when deciding whether these new techniques should be permitted. Detailed considerations of the questions raised in the consultation are provided below.

Permissibility of the new techniques

8. The Secretary of State for Health asked the HFEA to carry out a scientific review of the techniques in February 2011. The review panel concluded that the techniques are potentially useful for a specific group of patients whose offspring

² The Academy of Medical Sciences (2012). *Statement on mitochondrial diseases*. <http://www.acmedsci.ac.uk/p118pressid87.html>.

may have severe or lethal genetic disease, and recommended that further research be undertaken to provide further safety information and knowledge about the biology of human mitochondria.³ The review outlined the following three recommendations for future research to demonstrate the safety and efficacy of the techniques:

- Conduct MST using human oocytes (eggs) that are then fertilised.
- Conduct PNT using normally fertilised human embryos.
- Use PNT to raise healthy offspring in a NHP model.

Since the review was published, a recent study demonstrated the feasibility of MST using human oocytes.⁴ PNT has previously been successfully performed with abnormally fertilised human embryos⁵ and research is currently underway at the Wellcome Trust Centre for Mitochondrial Research at Newcastle University to investigate whether PNT is also feasible in normally fertilised embryos.

9. We are not aware of any group currently conducting research that would demonstrate that PNT can be used to safely produce offspring free from mitochondrial disease in a NHP model. However, a recent study has highlighted differences in fertilisation success rates using MST between NHP models and human oocytes, which has given rise to uncertainty about how applicable primate models are to mitochondria replacement approaches in humans.⁶ We understand that the DH intends to ask the HFEA to update the scientific review on the safety and efficacy of the techniques based on the latest evidence to sit alongside the HFEA report on the public consultation. Given the uncertainty raised about the value of further NHP research, and the time lapse since the scientific review, we strongly welcome this. This should include detailed consideration of whether NHP research should remain a prerequisite for the introduction of the treatment in humans.
10. We do not think that the two approaches to the prevention of mitochondrial disease should be differentiated between at this point. The public discussion highlighted that there was a desire to know more about the scientific evidence base in regard to the comparative safety and efficacy of the two techniques in development. However, we believe that it is important to recognise that these techniques are still at the research stage, and that there are not sufficient data available to date to determine whether MST or PNT in humans will differ in terms of producing embryos with lower levels of heteroplasmy (the proportion of mutated to normal mtDNA in a cell), successful fertilisation rates, overall health of offspring, or cost-effectiveness. As long as future research does not rule out the application of either technique on the grounds of safety or feasibility, we consider that the development of PNT and MST should proceed in order to allow for the useful comparison of the viability of both of these as potential clinical treatments.

³ Haites N & Lovell-Badge R (2011). *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception*. <http://www.hfea.gov.uk/6372.html>.

⁴ Tachibana, *et al.* (2012). Towards germline gene therapy of inherited mitochondrial diseases. *Nature*, doi:10.1038/nature11647.

⁵ Craven *et al.* (2010). Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature*, 465: 82-87.

⁶ Tachibana, *et al.* (2012). Towards germline gene therapy of inherited mitochondrial diseases. *Nature*, doi:10.1038/nature11647.

11. In June 2012, the Nuffield Council on Bioethics concluded that it would be ethical for families to opt to use the techniques to avoid the transmission of mitochondrial disease, if the techniques are shown to be safe and effective treatments.⁷ In line with this, and the scientific evidence above, the Academy would advocate the introduction of both techniques as treatments in humans for the prevention of serious mitochondrial diseases, providing ongoing research shows these to be safe and effective.

Changing the germline

12. The public discussion that we held indicated that some people do have concerns about permitting germline therapy. Although mitochondria replacement is a form of germline therapy, it is very limited in range and evidence indicates that MST and PNT are unlikely to have a functional impact on characteristics of offspring born with the aid of the techniques, beyond the mitochondria's role in energy production. Although it is not possible to rule out that this form of germline therapy would have unknown or unforeseen effects on nuclear DNA expression (via gene-gene interactions, for example), any effects are unlikely to be significant. Furthermore, no form of genetic modification or therapy aimed at specific genes (mitochondrial or nuclear) takes place as part of mitochondria replacement.

13. The Academy supports the view described by the Nuffield Council on Bioethics review, which reported that germline therapy that replaces mutated mtDNA represents a distinct material difference from nuclear transfer or nuclear modification technologies.⁸ Therefore, we do not consider that mitochondria replacement should be considered a green light (or a 'slippery slope') to the future adoption of germline therapies that could alter nuclear DNA.

The status of the mitochondria donor

14. In line with the findings of the Nuffield Council on Bioethics, we acknowledge that gamete donors may take on a wide variety of social roles (albeit often of a very restricted nature) in relation to the children born and the recipient families, which reflects the legal framework and diverse attitudes towards donation found in individuals and families. In relation to mitochondria donation however, we consider that it is important to recognise that the donor would only be making a nominal genetic contribution to a child who is born with the aid of mitochondrial replacement, i.e. only genes that affect energy production. As such, in terms of the biological contribution, bone marrow donation, which also incorporates third-party genes into patients' bodies in order to improve health, may be a more accurate analogy than gamete donation, where half of the child's genomic DNA and characteristics would be shared with the donor.

15. On the basis of the biological contribution of mtDNA to the child's overall genetic composition, we do not consider the status of the mitochondria donor to equate

⁷ The Nuffield Council on Bioethics (2012). *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*. <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders>.

⁸ Ibid.

to the status of a gamete donor. Accordingly, we do not consider that the regulatory framework that applies to gamete donation, in terms of making identifying information about donors available to donor conceived children when they are 18 years old, should be applied to mitochondrial donors without clear justification.

16. We would also highlight that some members of the public that attended the engagement event were keen to stress the diverse contemporary understandings of family and kinship, of which genetic inheritance is only one aspect. Furthermore, we are aware that the Nuffield Council on Bioethics is currently examining the ethical issues surrounding the disclosure of information about donor conception, and hope that this will include an examination of mitochondria donation. This is due to be published in spring 2013 and should it discuss mitochondria donation, we would recommend that this report is fully considered by the DH when examining evidence to do with the issue of mitochondria replacement techniques.
17. Should mitochondria donors have their anonymity preserved, a localised record of the donor should be retained, separate from the HFEA Registry (which contains identifying information about donors and is open to donor conceived children when they are 18), to ensure safety and traceability, in line with good practice for other tissue tracing processes.

Regulation of mitochondria replacement

18. The HFEA has already licensed preimplantation genetic diagnosis (PGD) for mitochondrial diseases in the UK. This is the best approach for reducing a mother's chance of passing on mitochondrial disease which results from mutations of nuclear DNA (in these instances, mitochondria replacement would not be applicable). PGD can also be used in some cases of maternal heteroplasmy to identify those embryos that are unlikely to manifest mitochondrial disease from mutations in mtDNA; however, it does not result in embryos free from abnormal mtDNA. Rather, a level of heteroplasmy is chosen as a practical threshold to select embryos that are believed to be at the lowest risk of developing mitochondrial disorder, based on the type of disorder and the available data about the likelihood of disease free lifespan. Consequently, PGD can only be used to reduce, but not eliminate, the risk of transmitting abnormal mtDNA that may lead to a mitochondrial disease, and it is only suitable for some, but not all, patients who suffer from mutations in their mtDNA - cases where the level of heteroplasmy is high or near complete (homoplasmy) are unsuitable. Furthermore, although there has been some concern that PNT and MST will result in 'carry over', where mutated mtDNA is transferred from the mother's egg to the donor egg alongside the nuclear DNA in the pronuclei or spindle, current evidence indicates that both techniques produce a much lower level of heteroplasmy in comparison to that currently accepted using PGD. As such, some women who carry mutated mtDNA and wish to have genetically related children would clearly benefit from these new approaches, which would eliminate the risk of mitochondrial disease.

19. There are substantive difficulties in assessing the likelihood that mitochondrial disorders may arise in offspring and the subsequent severity of the disease. For example, although some women may have multiple children who die from mitochondrial disease in early childhood, other women may have a child whose condition is relatively mild in childhood, but who goes on to suffer from a serious burden of disease later in life, such as mitochondrial myopathy. Consequently, although there are precedents for each of the regulatory options outlined in the consultation questions, we think that it would be very difficult for a regulator to decide which types of mitochondrial diseases are serious enough to allow mitochondria replacement and / or when it is appropriate in individual cases. As such, we would not recommend that the regulating body should require every couple requesting PNT or MST to be individually assessed by the HFEA to determine if their risk is 'serious'. Rather, we would be supportive of patients considering their reproductive options being enabled to make their own choices as to whether mitochondria replacement is their best available option (and if so, which technique is preferred), subject to all safety and efficacy requirements being met. This should follow comprehensive advice offered by clinicians with relevant expertise as to the full range of choices available to them, such as PGD, mitochondria replacement, oocyte donation, or adoption.
20. However, to safeguard patients from the promotion of mitochondria replacement by private-sector services where the approach may not be relevant (i.e. where the risk of having a child who would inherit a disorder that results from mutated mtDNA is very low or negligible), we would recommend that mitochondria replacement treatments should only be made available after the patient has been referred for treatment by a centre with appropriate expertise in mitochondrial disease. The HFEA could maintain a list of approved referrers who are able to refer patients for mitochondria replacement treatments. This should follow advice from the mitochondrial community, but one option would be for it to be based around the NHS Rare Mitochondrial Disease Service for Adults and Children, which includes centres at Newcastle, London and Oxford.
21. In the Academy's response to the DH's consultation on proposals to transfer functions from the HFEA and the Human Tissue Authority, we highlighted the need for closer oversight of the introduction of new assisted reproductive technologies (ARTs).⁹ Therefore, we would strongly recommend that the HFEA should require clinical evaluation as a condition of licensing these techniques as treatments. Clinics should be required by law to record and report detailed information in relation to each treatment cycle involving mitochondria replacement to the HFEA on a regular basis. Requiring clinics to report additional data to that routinely collected by the HFEA for all IVF treatment cycles would reflect the licensing guidance issued by the HFEA for PGD in 2003 following public consultation on the clinical use of PGD and the recommendations of the Joint Working Party of the HFEA and the Human Genetics Commission.¹⁰
22. If mitochondria replacement techniques are licensed as treatments to prevent the transmission of serious mitochondrial disease, this would represent the first form

⁹ The Academy of Medical Sciences (2012) *Response to the Department of Health consultation on proposals to transfer functions from the Human Fertilisation and Embryology Authority and Human Tissue Authority*. <http://www.acmedsci.ac.uk/p100puid254.html>.

¹⁰ The Human Fertilisation & Embryology Authority (2003). *CH(03)04: Guidance on Preimplantation Testing*. <http://www.hfea.gov.uk/2686.html>.

of germline therapy introduced into clinical practice. Consequently, it is imperative that long-term and trans-generational follow-up of any offspring born following the use of these techniques is conducted. However, in order to enable these follow-up studies to be conducted effectively, it is essential that patients and their partners consent to participate in long-term follow-up at the time they are considering using these techniques. Taking this into consideration, we would highlight the recommendation made by a 2004 report by the Medical Research Council, which stressed the need for more effective data gathering and coordination processes to be set up by the HFEA in close collaboration with the NHS and ART clinics, to monitor the immediate and long-term health of all children conceived through ART and their mothers.¹¹ The report emphasised that it is crucial to fully explore the ethical issues around obtaining consent to access such data and that approaches should be discussed with ART patients and clinics to examine what influences people to give or withhold consent and their views about the need for, and acceptability, of such research. This process should identify the optimal methods of ensuring follow-up takes place and define the standards that are to be met. Treatment licences for these techniques should then only be granted to clinics that have documented plans for the long-term follow-up of offspring in place, which meet these standards. Assessing the implementation of this plan should be part of the inspection process carried out by the HFEA. Our Fellows would be willing to participate in further discussion about how to achieve effective long-term follow-up.

23. There should be appropriate oversight of the HFEA to ensure that effective follow-up of the techniques' efficacies and safety is being carried out. The MRC report highlighted that both the National Institute for Clinical Excellence and the Health Technology Assessment Programme (now part of the National Institutes of Health Research) would be well placed to contribute to additional independent evaluation and monitoring of the safety and outcome of ARTs whenever necessary.

Should the law be changed?

24. After considering the scientific issues to do with the potential introduction of the mitochondria replacement techniques (with attention paid to the ethical issues that have been raised), **the Academy is in full support of introducing regulations to enable these techniques to be used to prevent the transmission of serious mitochondrial disease.** We would advocate that Parliament amend the Human Fertilisation and Embryology Act 1990 (as amended) to enable the use of these new techniques in the clinic. If Parliament supports an amendment to the legislative framework to allow the use of these techniques in principle, **further research should continue to investigate their safety and efficacy** to enable the HFEA to make an informed decision as to their first introduction into the clinic. If the regulatory functions of the HFEA are transferred to another regulatory body, it is important that a comprehensive regulatory framework is kept in place that will safeguard the interests and wellbeing of prospective parents, donors of mitochondria and potential offspring that may result from either technique.

¹¹ The Medical Research Council (2004). *Assisted Reproduction: a safe, sound future.*
<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002393>.

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