

# Human Fertilisation and Embryology Authority: (HFEA): Medical Frontiers: Debating Mitochondria Replacement

## Response by the Wellcome Trust

December 2012

### INTRODUCTION

1. The Wellcome Trust (the Trust) is pleased to respond to the HFEA's consultation 'Medical Frontiers: Debating Mitochondria Replacement'. As a major research funder, and facilitator of public discussion, deliberation and debate of ethical issues around emerging techniques to prevent inherited mitochondrial disorders, we welcome the opportunity to respond to this consultation.
2. The Trust is dedicated to achieving extraordinary and lasting improvements in human and animal health. As a funder of important research into understanding mitochondrial DNA ('mtDNA') and, more specifically, research into techniques to prevent inherited mitochondrial disorders, we are committed to ensuring that sufferers of mitochondrial disorders can benefit from the outputs of our research.
3. The impact of mitochondrial disorders is wide ranging and in severe cases can lead to miscarriage, still birth, early infant death, or chronic illness and death in childhood or adulthood. A particularly moving example of the impact of these devastating disorders on families is the story of Sharon Benardi who has lost seven children to mitochondrial disorders.<sup>1</sup>
4. The important world-class research we support in this field seeks to develop methods of preventing the transfer of such diseases to future generations. This research - subject to appropriate regulations - will also advance the development of treatments for those, often very young, patients who currently suffer from the diseases.
5. Based on both scientific evidence and ethical considerations to date, we encourage the Government to introduce regulations which will enable the HFEA to license the use of techniques in the clinic which will enable women who carry mitochondrial disease to choose to have children unaffected by these devastating disorders.
6. Our responses to the specific questions are set out below:

**Permissibility of new techniques:** *Having read the information on this website about the two mitochondria replacement techniques – maternal spindle transfer and*

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<sup>1</sup> <http://www.bbc.co.uk/news/magazine-19648992>

*pro- nuclear transfer, what are your views on offering (one or both of) these techniques to people at risk of passing on mitochondrial disease to their child? You may wish to address the two techniques separately.*

7. The nature of science is such that avenues to explore both techniques need to remain open so that the effectiveness and safety of each technique can be compared. Exploration of each technique has already led to insights into mitochondria and developmental biology which will benefit other areas of research, and can be expected to continue to do so in the future.
8. We concur with the Nuffield Council on Bioethics that if both maternal spindle transfer (MST) and pro-nuclear transfer (PNT) are proven to be 'safe and effective' then it would be ethical for families wishing to use them to do so.<sup>2</sup> The HFEA Scientific Review of these techniques concluded that both techniques are potentially useful for specific cases of mitochondrial disease and that there is currently no evidence to suggest that the 'techniques are unsafe'.<sup>3</sup> It may be that further research will find one technique more effective for some patients more than others; thus it is important that work is allowed to proceed using both techniques, so that the most clinically appropriate option is available to be offered to patients.
9. The Nuffield Council further concluded that neither technique is ethically preferable and it is likely to be necessary to gather information about both techniques in order to identify which technique might offer the most effective treatment.<sup>4</sup> This is a role the Trust is fulfilling in funding research in this field.
10. We join the Nuffield Council in rejecting the view, advanced by some opponents of this technology, that PNT is a form of cloning. We agree with the Nuffield Council conclusion that the 'clear material difference' between mitochondrial and nuclear genes differentiates these techniques from genetic cloning. Further, PNT does not transfer or 'clone' a pre-existing fully formed nucleus and there is no manipulation of the pronuclei as would be required in a 'cloning' technique.<sup>5</sup>

**Changing the germ line:** *Do you think there are social and ethical implications to changing the germ line in the way the techniques do? If so, what are they?*

11. We believe that any social and ethical implications extending from the proposed techniques to change germ line mitochondrial genes are far outweighed by the benefits resulting from the birth of a healthy child. These therapies replace, rather than modify, diseased mitochondria with healthy mitochondria which can be passed on to future generations. We believe

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<sup>2</sup> <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders> at paragraph 5.2

<sup>3</sup> <http://www.hfea.gov.uk/6372.html>

<sup>4</sup> <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders> at paragraph 5.4

<sup>5</sup> <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders> at paragraph 4.60

most families affected by mitochondrial disorders will consider it desirable that the technique will protect not only their own children, but future generations.

12. We do not believe that changing the germ line in the way the techniques do raises unacceptable ethical concern, because the alternative is that 'natural' diseased mtDNA that has not been altered using these techniques will be passed on to future generations, with serious negative effects on their health. As others have concluded, enabling future generations to produce children with healthy mitochondria is 'hardly a bad thing'<sup>6</sup>. Further, the techniques are not known to or intended to interfere with the nuclear genome.
13. In our view, there is an ethical imperative that women who carry mitochondrial disease and wish to have their own children are offered the choice of undergoing these techniques to prevent the transmission of mitochondrial disorders, if they are found to be safe and effective. These techniques could help avoid diseases which often lead to suffering on the part of the affected child and their family, early death or prolonged disabilities which require significant care. They also promise to allow parents in this generation, and their female offspring, to have children without the psychological distress of knowing they might be passing on a devastating disease.
14. We do not believe the techniques will open the door to more widespread germline<sup>7</sup> genetic engineering for two reasons. Firstly, these techniques limit germline manipulation to genes of the mitochondria, which are involved solely in programming the functions of these organelles. Secondly, the techniques will not induce germline changes to nuclear DNA, which programmes all the other functions of the organism. These techniques are not suitable for germline manipulation of nuclear DNA, and thus have few implications for this more significant ethical question.

**Implications for identity:** *Considering the possible impact of mitochondria replacement on a person's sense of identity, do you think there are social and ethical implications? If so, what are they?*

15. MtDNA, which is the only type of genetic material altered by these techniques, encodes just 37 of the 22,000 human genes, or less than 0.002 per cent of the total. These genes exist outside the nucleus purely to programme mitochondria to provide energy for cells, and do not govern other cellular or bodily functions that are normally associated with identity and character. As only a tiny quantity of DNA, involved only in energy functions, is altered, and as nuclear DNA is unaffected, we do not believe these techniques raise significant social or ethical issues about a person's sense of identity. An analogy could be drawn with replacing the battery in a camera - the brand of the battery does not affect the characteristics of the camera's functions.

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<sup>6</sup> North East England Stem Cell Institute (2008) *Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation.*

<sup>7</sup> Germline genetic engineering is where the genetic changes to an egg or embryo are inheritable and therefore passed on to succeeding generations. The technique is controversial because of its potential for human enhancement.

16. The Nuffield Council on Bioethics considered the issue of identity in some depth in their report.<sup>8</sup> The report concluded that the changes to a child's genetic profile as a result of these techniques cannot be assumed to affect their conception of 'who they are' and that it would be wrong to see the mitochondrial donor as a 'third genetic parent'. We concur with this view. Again, in this case, the outcomes and impact on a child born free of mitochondrial disease and their family are such that, in our opinion, there would be greater ethical implications in not making such treatments available.
17. Similar concerns regarding identity were initially raised with respect to children born by IVF<sup>9</sup> and children born through egg or sperm donation. However, research into the nature of such families, such as that led by Professor Susan Golombok, of the Centre for Family Research in Cambridge, has found that these families generally function very well. Professor Golombok, indeed, points out that individuals born after gamete donation are likely to consider their donors to be more important to their identity than would individuals born after mitochondrial donation, because of the far greater proportion of genetic material they receive from a donor. Individuals born after gamete donation receive 50 per cent of their genes from a donor, who is not one of their social parents, while individuals born after mitochondrial donation will still receive more than 99.9 per cent of their genes from their social parents, with only 37 genes originating from their donor.<sup>10</sup>
18. We therefore consider that mitochondrial transfer techniques are likely to raise far fewer social and ethical issues surrounding offspring identity than are already raised by existing fertility techniques that are widely accepted, such as gamete donation and surrogacy.

**The status of the mitochondria donor:** *In your view how does the donation of mitochondria compare to existing types of donation? Please specify what you think this means for the status of a mitochondria donor. Thinking about your response, what information about the mitochondria donor do you think a child should have? (Choose one response only):*

- i. The child should get no information*
- ii. The child should be able to get medical and personal information about the mitochondria donor, but never know their identity*
- iii. The child should be able to get medical and personal information about the mitochondria donor and be able to contact them once the child reaches the age of 18*
- iv. I do not think mitochondria replacement should be permitted in treatment at all*  
*Please explain your choice.*

19. We believe mitochondrial donation should be distinguished from sperm and egg donations where the resulting child would receive 50 per cent of their genes from

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<sup>8</sup> <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders>

<sup>9</sup> <http://www.ncbi.nlm.nih.gov/pubmed/11333087>

<sup>10</sup> <http://www.wellcome.ac.uk/News/2012/Features/WTVM055438.htm>

a donor. As detailed above, a mitochondrial donor contributes significantly less both socially and genetically to the resulting child. We therefore suggest option 2 above, though we would wish to add the qualifier that details regarding the mitochondria donor should remain anonymous, unless the donor is already known to the recipient. The choice should remain open to patients to use a known donor, for example a relative or friend with healthy mitochondria, if appropriate.

20. Data on the donated mitochondria, including identification of the donor, should be kept for longer-term follow up and may be of longer-term medical utility for research purposes and for the individual's own medical history. It will also be crucial to ensure that a robust mechanism is in place for long-term follow up of any children born following use of these techniques. The Nuffield Council on Bioethics reached the same conclusion in its ethical review of mitochondrial donation.

**Regulation of mitochondria replacement:** *If the law changed to allow mitochondria replacement to take place in a specialist clinic regulated by the HFEA, how should decisions be made on who can access this treatment? (Choose one response only)*

- i. Clinics and their patients should decide when mitochondria replacement is appropriate in individual cases*
- ii. The regulator should decide which mitochondrial diseases are serious enough to require mitochondria replacement and, just for these diseases, permit clinics and patients to decide when it is appropriate in individual cases*
- iii. The regulator should decide which mitochondrial diseases are serious enough to require mitochondria replacement and also decide, just for these diseases, when it is appropriate in individual cases*
- iv. I do not think mitochondria replacement should be permitted in treatment at all*

*Please explain your choice.*

21. Clinics and their patients should decide when mitochondria replacement is appropriate in individual cases. In our opinion, the most appropriate people to make decisions as to when mitochondria replacement techniques are both socially and ethically appropriate are the individual patient and their families in consultation with their consulting specialists. These specialists could include IVF clinics and clinicians and mitochondrial geneticists.

22. The techniques will not be suitable for all patients with diseased mitochondria and it is crucial that clinicians with appropriate expertise in mitochondrial genetics are given the ultimate say in when these techniques should be used. If these techniques are to be introduced into the clinic, we would expect best practice guidelines, similar to those that currently apply to IVF, to also apply to these techniques and to the donation of mitochondria.

**Should the law be changed:** *In Question 1, we asked for your views on the mitochondria replacement techniques MST and PNT. Please could you now tell us if you think the law should be changed to allow (one or both of) these techniques to be made available to people who are at risk of passing on mitochondrial disease to their child?*

23. We believe the regulations should be introduced to enable both of these techniques to be licensed for therapeutic use by the HFEA to benefit people who are at risk of passing on mitochondrial disease to their child. The Human Fertilisation and Embryology Act (2008) (the 'Act') explicitly anticipated this possibility by introducing provisions to allow research to develop techniques to prevent transmission of mitochondrial disease, and to allow these to be approved for clinical use without fresh primary legislation. Parliament did not make such regulations at the time as it was thought these techniques were some way off entering the clinic and would require further consideration and ethical debate.
24. Parliament clearly envisaged clinical use to result from this research, through the inclusion of a regulation making power. This power enables the Secretary of State to make regulations to amend the definition of a 'permitted embryo' or 'permitted egg' to include one which has had applied to it in a 'prescribed circumstance', a 'prescribed process' to 'prevent the transmission of serious mitochondrial disease'.<sup>11</sup>
25. The legal framework to allow clinical use of these procedures must be put into place at the earliest opportunity, so that the parliamentary process required can run concurrently with the experiments that need to be completed before patients can be treated.
26. To delay the introduction of regulations until such experiments are complete would lead to a significant delay before patients can be treated, once the evidence suggests it will be sufficiently safe to do so. This will mean some families who might otherwise have been able to benefit from this technique would no longer be able to do so, as some women will be older and less fertile.
27. A decision to introduce regulations to enable the HFEA to license these techniques for therapy would not, in itself, open the way for them to be used in the clinic without further evidence of safety and effectiveness becoming available. Regulations would allow the HFEA to license techniques to avoid mitochondrial disease, and a licence would be awarded only with supporting evidence from research.

**Further considerations:** *Are there any other considerations you think decision makers should take into account when deciding whether or not to permit mitochondria replacement?*

28. Medical knowledge in this field has reached this current stage of

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<sup>11</sup> Section 3, Human Fertilisation and Embryology Act 2008

advancement as a result of world leading research which has been funded through public and charitable funders. Where techniques are developed and shown to be safe and effective, these must be made available to women to give them the choice of having children free of devastating mitochondrial disease. To do otherwise would deny the opportunity to prevent the transmission of this devastating disorder.

29. Objections have been raised against these techniques on the grounds that mitochondrial donation, and germline alterations to DNA, are “unnatural”. However, all medical interventions, including transplants, antibiotics, vaccines and even setting of broken bones, are to a greater or lesser extent unnatural. What these procedures, and mitochondrial donation, have in common is that they offer the potential for humanity to overcome the cruelties of nature, and to offer people affected by disease the chance of a healthier life.
30. When new medical treatments are given to human beings for the first time, it is never possible to be certain that these will be 100 per cent safe or effective. Even the most exhaustive research can establish only that a technique is sufficiently likely to be safe to justify first-in-man clinical use in a research setting. If medicine is to progress, however, doctors must be permitted to use new techniques when evidence suggests these are indeed sufficiently safe and effective to use on patients for the first time. In the case of mitochondrial donation, there will be much more evidence for safety and effectiveness available before the first clinical use than was available for many other techniques, such as organ transplants and IVF.
31. The Wellcome Trust has run two public engagement activities about mitochondrial transfer techniques during the consultation period, which have revealed broadly positive public attitudes towards the technology. In October, we partnered with Mumsnet to run an open question and answer session with Professor Doug Turnbull and Professor Susan Golombok. The Mumsnet users who participated were overwhelmingly supportive of the techniques. Typical comments included:
- "I'm all in favour of wiping out these horrific diseases that cause tremendous suffering. Good luck to the scientists."  
"I think it is a fantastic breakthrough. Well done Newcastle."  
"How can anyone seriously say there are "ethical issues" about some vague squeemishness that DNA has come from 3 people being of comparable concern to the suffering of that poor mother who had to watch both her sons die?"
32. The engagement is archived here:  
[http://www.mumsnet.com/Talk/general\\_health/a1577432-Q-A-about-the-ethics-of-using-new-IVF-techniques-to-prevent-children-inheriting-incurable-genetic-conditions-ANSWERS-BACK](http://www.mumsnet.com/Talk/general_health/a1577432-Q-A-about-the-ethics-of-using-new-IVF-techniques-to-prevent-children-inheriting-incurable-genetic-conditions-ANSWERS-BACK)
33. Responses to the users' questions are here:

<http://www.mumsnet.com/qanda/preventing-mitochondrial-disease-ivf>

34. The Trust also organised a public event at the Cheltenham Literature Festival on October 14, involving Professor Turnbull, Professor Golombok and the philosopher Julian Baggini. Around 100 people attended, and a straw poll revealed about 90 per cent support for the techniques, with a few people wanting more information and only one audience member opposed.
35. We also note the result of a straw poll conducted by BBC Radio 4's Any Questions on September 22, at which the audience was asked whether they supported approval of mitochondrial transfer techniques, whether they were against, or whether they were more information. Jonathan Dimbleby, the presenter, reported that almost half the audience was supportive, almost half wanted more information, and only about 5 per cent were opposed.
36. The programme is available here: <http://www.bbc.co.uk/programmes/b01mqr5q>