This response was submitted to the call for evidence by the Nuffield Council on Bioethics on *Emerging techniques to prevent inherited mitochondrial disorders: ethical issues* between January 2012 and February 2012. The views expressed are solely those of the respondent(s) and not those of the Council.

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TECHNIQUES TO PREVENT INHERITED MITOCHONDRIAL DISORDERS:

ETHICAL ISSUES

1. BACKGROUND

(a) The Human Fertilisation and Embryology Act 2008 makes provision through Regulations (under new section 3ZA(5)), to permit the implantation into a woman of embryos or eggs that have been altered, if it is to prevent the transmission of mitochondrial disease. This potentially includes alterations in nuclear and /or mitochondrial DNA, reproductive cloning and permitting cells to be added to the embryo other than by division of the embryo's own cells, provided that:

> *…the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease.*

(b) There is a wide variety of potential alterations that could be made in eggs or embryos to prevent transmission of mitochondrial disease, subject to the conditions given in new section 3ZA(5), since the strict prohibitions in the HFE Act 2008 against implanting embryos or gametes in a woman that have been altered in any way, can potentially be removed under these Regulations.

(c) It is currently proposed to use either oocyte nucleus transfer (maternal spindle transfer, or MST) or pronuclear transfer (PNT) to prevent the transmission of mitochondrial disease. This would be relevant for mitochondrial disease that was caused by defects in mitochondrial DNA.

(d) However, there is much less Parliamentary scrutiny in passing Regulations than there is in passing primary legislation. No amendments would be permitted to the proposed Regulations and only a short debate would be permitted in Parliament. This is inadequate in a matter of such significance as the current proposals since they involve germline genetic modification, cell nuclear transfer, and the introduction of DNA from two women into an embryo that is to be implanted, resulting in systemic alteration of DNA in the child that is produced.

2. PATIENTS WITH MITOCHONDRIAL DISEASE WOULD NOT BE IMPROVED OR CURED BY MITOCHONDRIAL TRANSFER TECHNIQUES

(a) A misleading impression may be received by the public that patients with dreadful mitochondrial diseases could be treated or even cured by maternal spindle transfer or pronuclear transfer techniques. However, this is not the case. These procedures do not treat the mitochondrial disease in the patient. The only reason for this technique being used would be if a woman wished to have a genetic child of her own.

(b)When informing the public, it is important that it is clear that the patients themselves do not have any improvement in their symptoms or any cure, in order that there is clarity about what it is hoped these techniques may (if they worked) and may not do.

3. PRONUCLEAR TRANSFER cf MATERNAL SPINDLE TRANSFER

(a) Both cell nuclear transfer techniques proposed would mean that the resulting child would have nuclear DNA from both the mother and the father and mitochondrial genes from a second woman. This could cause what has been termed 'genetic bewilderment.'

(b) Both techniques would result in germline genetic modification (of mitochondrial DNA), resulting in systemic alteration of DNA.

(c) Pronuclear transfer would also involve the destruction of an embryo.

4. RISKS

(a) The health risk is borne entirely by the *child,* not the parent.

The health risks of carrying out IVF and maternal spindle transfer or pronuclear transfer would be borne entirely by the child conceived via these procedures. Health risks are themselves an ethical issue.

(b) Health risks

(i) Heteroplasmy.
Some of the deficient mitochondria from the woman with mitochondrial disease may be transferred to the enucleated egg, causing mitochondrial heteroplasmy. This could result in mitochondrial disease developing either in the child or in future generations. Although Craven et al (2010)[1] found that embryos created by transfer of pronuclei using abnormally fertilised eggs had less than 2% carry-over of mitochondrial DNA and some had no detectable carry-over, as pointed out in the Nuffield '*Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception*' there is evidence that at least in some cases there can unexpectedly be preferential multiplication of unhealthy mitochondria. Craven et al were unable to investigate this. However, if preferential multiplication were to occur, it could increase the risk of mitochondrial disease either in the child over time, or in future generations.

(ii) Emergence of health defects with age:
There are concerns that cell nuclear transfer techniques could cause modification of the epigenome. Individual genes can be differentially affected and changes in the epigenome can be very subtle, but have a devastating effect. Some health defects caused by epigenetic factors emerge later in life, so may not be immediately obvious.

(iii) Transmission of health defects caused by cell nuclear transfer techniques to subsequent generations:
There is a concern that any health defects caused by cell nuclear
transfer procedures could be passed on through subsequent generations, since maternal spindle transfer and pronuclear transfer result in germline genetic modification.

(iv) Non-human primates:
It has been emphasised that experiments in non-human primates would have to be carried out in order to assess the health risks of cell nuclear transfer techniques. Tachibana et al (2009)[2] have carried out maternal spindle transfer using healthy eggs from non-human primates (rhesus macaques). Some of the resulting embryos were successful and produced healthy offspring. However, since problems may develop later in life, or in their own offspring, long-term studies are required in order to assess the safety of the procedure. The experiment with non-human primates needs to be repeated using pronuclear transfer between embryos and long-term studies need to be carried out, in order to assess the safety of that procedure also, since there may be different epigenetic effects and differing degrees of heteroplasmy etc.

5. SLIPPERY SLOPE:

(a) Slippery slope:
In addition to the ethical issues surrounding the cell nuclear transfer techniques proposed (maternal spindle transfer and pronuclear transfer), there are genuine concerns about the proverbial 'slippery slope':

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[1] Craven, L. et al (2010). Nature 465:82-85. 'Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease.'
[2] Tachibana, M. et al (2009) Nature **461**:367-372. '*Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells.'*

(b) Reproductive Cloning – Mitochondrial Diseases caused by defects in Mitochondrial DNA

(i) *Blastomere transfer*:
Blastomere transfer - acknowledged by Bredenoord et al (2011) to be reproductive (embryo) cloning – has already been proposed by them as an alternative to maternal spindle transfer or pronuclear transfer.[3] The suggestion is made that other nuclear transfer techniques are attempted first, owing to the fact that blastomere transfer '*may lead to more complex ethical appraisals than the other variants;'* nevertheless it is promoted as a potential way to prevent the transmission of mitochondrial disease.

(ii) *Reproductive Cloning*:
Bredenoord et al conclude about blastomere transfer that:
'… if this variant were to become safe and effective, dismissing it because it would involve reproductive cloning is unjustified.'

The Human Fertilisation and Embryology Act 2008 repealed the Reproductive Cloning Act 2001. Prior to this, reproductive embryo cloning as proposed by Bredenoord et al, would have been caught by the Reproductive Cloning Act 2001, however this would no longer be 4
the case. Should Parliament decide in the future to pass Regulations permitting this under section 3ZA(5), then reproductive embryo cloning could be made legal.

Similarly, somatic cell nuclear transfer (SCNT), although very unlikely to be proposed currently as a way to prevent the transmission of mitochondrial disease because of safety concerns and practical difficulties, is nevertheless potentially another cell nuclear transfer technique that could be used in the case of mitochondrial disease caused by defects in mitochondrial DNA. As for reproductive embryo cloning, somatic cell nuclear transfer ('traditional' cloning), would also no longer be caught by the obsolete Reproductive Cloning Act.

Although no-one would currently suggest SCNT as a way of preventing the transmission of mitochondrial diseases caused by defects in mitochondrial DNA since other cell nuclear transfer techniques are currently preferred, there are clear signs of a slippery slope already, since reproductive embryo cloning has been proposed.

(c) Germline Genetic Modification – Mitochondrial Diseases caused by defects in Nuclear DNA

(i) Many mitochondrial diseases are caused by defects in nuclear, rather than mitochondrial DNA. There is already provision in the HFE Act to permit pre-implantation genetic diagnosis for these diseases. However, there is also provision to make Regulations under section 3ZA(5) that would permit germline genetic engineering of nuclear DNA if it was for the purpose of preventing the transmission of mitochondrial disease. Since Regulations made under section 3ZA(5) could prescribe a process that altered nuclear DNA in eggs or embryos, they would be redefined in legal terms as 'permitted' eggs and embryos, thus allowing them to be implanted in a woman. This potential alternative to PGD would be germline genetic engineering of nuclear DNA – probably an unintended consequence of the wording of section 3ZA(5).

(ii) Although germline genetic engineering of nuclear DNA is not currently proposed, if alteration of mitochondrial genes whether by maternal spindle transfer or pronuclear transfer were to be permitted, it would set a precedent of altering heritable characteristics and genetic material, and would open the door to germline genetic engineering in general: although it has been argued by some that altering mitochondrial genes is completely different scientifically and ethically from altering nuclear genes, one can easily foresee pressure from other patient groups with genetic diseases caused by defective nuclear DNA. The fine-tuning of whether genes are nuclear or mitochondrial might seem irrelevant: if one patient group may have systemic alterations in the genes of their children, it might be argued, then why not another?

[3] Bredenoord et al (2011). RMB Online Feb;22(2):200-7. Epub 2010 Nov 12. '*Nuclear transfer to prevent mitochondrial DNA disorders: revisiting the debate on reproductive cloning.'*

(iii) If alterations in mitochondrial DNA via maternal spindle transfer or pronuclear transfer were permitted to prevent inheritance of mitochondrial disease caused by mitochondrial DNA, then it is very probable that there would be pressure in the future to permit germline genetic engineering of nuclear DNA, initially via Regulations made under section 3ZA(5) of the HFE Act.

(d) Mitochondria and Cognition / Genes with a 'housekeeping' function:

(i) It has been argued that mitochondria are only 'batteries,' the organelles that produce most of the energy in cells, so there is no ethical problem in altering these genes. However, this may not be an entirely correct understanding of mitochondrial DNA, since it has been found that there is a link between mitochondrial DNA and cognition, including learning, exploration and sensory development in mice.[4],[5] Mitochondrial DNA may, therefore, be connected with personal characteristics, previously thought to be the sole preserve of nuclear DNA.

(ii) Moreover, the argument is a dangerous one, opening the way for additional genetic modification / enhancement. There are many genes considered to be 'housekeeping genes.' If genes for energy can be altered then why not, it could be argued, other 'housekeeping genes' (in nuclear DNA) which code for other useful functions?

6. ALTERNATIVES

The State does not have a *duty* to enable women to have their own genetic children. However, there are alternatives, in particular adoption. Egg donation is also an existing possibility. For mitochondrial diseases caused by defects in nuclear DNA (rather than mitochondrial DNA), PGD is possible. (These cases would in any event not be helped by mitochondrial transfer.)

7. CONCLUSION

There would be a number of disadvantages to permitting maternal spindle transfer or pronuclear transfer to prevent transmission of mitochondrial disease:

- Secondary legislation would be used to legalise the creation of children via cell nuclear transfer techniques, rather than primary legislation. Insufficient Parliamentary time would therefore be given for scrutiny of some profound ethical issues and intricate scientific detail, and there would be no opportunity to amend the proposed legislation.
- Germline genetic modification (of mitochondrial DNA)
- Systemic DNA alteration in a child
- 'Genetic bewilderment' in the resulting offspring, as a result of having nuclear genes from the mother, and crucial mitochondrial genes from another woman.
- With pronuclear transfer, there is also embryo destruction.
- Health risks to the child: the risks are borne by the child, not by the parents.
- Health risks may emerge throughout the lifetime of the child (epigenetics / heteroplasmy)
- Health problems caused by cell nuclear transfer techniques may emerge in the offspring of the children.
- There is a possibility that the cell nuclear transfer procedures may extend to reproductive embryo cloning - a procedure that has already been proposed - unless Regulations were clearly worded to avoid this.
- Altering heritable DNA in a child would set a precedent of permitting systemic alteration of DNA in a child from conception.
- There would be strong pressure to allow germline genetic modification of nuclear DNA initially for mitochondrial, and then for other, diseases caused by defects in nuclear DNA.

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[4] Roubertoux, P.L. et al (2003) Nat. Genet. **35**:65-69. '*Mitochondrial DNA Modifies Cognition in Interaction with the Nuclear Genome and Age in Mice.*'

[5] Moreno-Loshuertos, R. et al. (2006) Nat. Genet. **38**:1261-1268. '*Differences in Reactive Oxygen Species Production Explain the Phenotypes Associated with Common Mouse Mitochondrial DNA Variants.'*

- Adoption would be a possible alternative, although it is understood that some women may want their own genetic children.

Dr. Elizabeth Allan. 24.2.2012