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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Emerging techniques such as PNT and MST involve replacing the mitochondrial genes that a child would have received through natural conception, with mitochondrial genes taken from a healthy donor. Is it acceptable, in this instance, to select genes that will then be inherited by future generations?

I think it is ethically acceptable in this instance, to select genes that will then be inherited by future generations. The whole aim of the approach is to prevent transmission of disease.

PNT involves removing the two pronuclei from a very early embryo containing a significant level of mutated mitochondria, at the one-cell stage before the genetic material in the pronuclei of the sperm and egg cells merges to form the mature nucleus of the embryo. The pronuclei are transferred into another embryo at the same stage of development, which contains healthy mitochondria and which has had its pronuclei removed. From the two-cell stage of embryonic development onwards, the embryo's cells contain one nucleus combining both parents' DNA. What ethical distinctions can we make between prospective treatments which would:

a. transfer pronuclei between embryos?

b. transfer the nucleus of a cell between embryos?

c. seek to modify the nuclear DNA of an embryo?

I believe there are different ethical issues around the transfer of PNT and MST compared to modifying the nuclear DNA of an embryo. The techniques proposed are to prevent transmission of disease and will have no effect on the other characteristics of the child.

All new techniques pass through research stages before being offered for treatment, but in the early stages of treatment might still be considered experimental. Is it reasonable to use experimental techniques such as these in treatment?

All new therapies must move from the experimental stage to the treatment stage. A careful consideration of risk is important but also it is essential that we appreciate there is risk with many medical interventions. The risk of not having the treatment is considerable and this also has to be remembered

After the use of these techniques, children would inherit nuclear DNA (around 25,000 genes) from their parents, and mtDNA (13 genes) from the donor of the egg. What might the use of these techniques signify for the relationships of the resulting child to the three adults with whom it shares a genetic connection?

This is a question that is better answered by patients and families

How might mitochondrial DNA be associated with a person's identity?

Since mitochondrial DNA does not alter any characteristics essential to our identity – I do not think it is associated with identity

Could the relationships created between the people involved in these new techniques- particularly between the mitochondrial donor and a person born with their donated mitochondria- be seen as similar to those involved in:
a. organ or tissue transplantation?
b. gamete donation?
c. a donation of other bodily material?
Or, should these relationships been seen as unique?

I believe similar to a or c – tissue or blood donation

Only daughters born as a result of these techniques would be able to pass their mtDNA on to subsequent generations. Would it be reasonable to permit prospective parents using these technologies to also use pre-implantation sex selection (preferring male embryos), if they requested it in order to limit the risks of transmitting any adverse side effects of the techniques to future generations?

Please see confidential comments

If mitochondrial donation were to be approved for medical treatment in the UK, what government or regulatory policies, and/or professional guidelines would be needed to promote ethically sound practices?

I believe the existing legislation and regulatory framework is excellent – Parliament decides on the legislation and a license is awarded based on expert advice by HFEA (or other regulatory body)

If mitochondrial donation were not to be approved for translation from research into medical treatment in the UK, what ethical concerns, if any, would follow?

I believe the ethical concerns would be

1. That mothers go to another country for treatment where regulations and safety issues are not so stringently regulated as in the UK
2. We would be depriving families of reproductive choice

Is it desirable for a record of the donation to be kept and managed by the relevant authorities, and if so, what should be recorded and to whom should this information be made available?

The regulatory authority – as regards availability would be inclined to leave this up to individuals. If the mitochondrial donor wishes to remain anonymous then I would be tempted to allow this.

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requested it in order to limit the risks of transmitting any adverse side effects of the techniques to future generations?

This is a difficult and challenging area. The transmission of mitochondrial DNA disease is complex due to the genetic bottleneck present in oocyte development. The precise site of this bottleneck and timing is still debated, however that there can be a wide spread in mitochondrial DNA mutation load in different oocytes is well accepted. This means even starting with small amounts of mutated mtDNA it is possible for individual oocytes to contain high levels of mutated mtDNA. There is good evidence that in mothers with heteroplasmic mutations that the average mtDNA mutation loads in oocytes is the same as the load in the same woman. Thus the lower the level of mtDNA heteroplasmy in the mother correlates with less chance of transmitting high levels of an mtDNA mutation. Preliminary evidence from studies using pronuclear and metaphase II transfer have shown that there are very low levels in both embryos and offspring (for metaphase II transfer).

There is a potential complicating factor which could influence the level in oocytes. The committee will be aware that Shoubridge and colleagues have shown that in heteroplasmic mice carrying two different mitochondrial genotypes (BALB and NZB) there was directional segregation of the genotypes in different tissues. This raises the possibility that this might happen in humans. However, there are major differences between humans and inbred mouse strains. The most important difference is that humans are out bred with much mixing of different ethnic groups and indeed even within groups. I believe this makes directional segregation much less likely. Experiments looking at segregation in the cells within the developing blastocyst will not allow us to explore the issue associated with replication, although cultured ES cells might. Primate experiments could be of some help but these would need to be carefully considered and determine if the primates are also out bred.

From an ethical perspective I do not feel comfortable about sex selection based on a hypothetical risk. It maybe that all viable embryos are female, this I think would create an almost impossible dilemma for the mother. In addition, we are assuming that in 20 - 50 years our ability to treat mitochondrial diseases has not moved forward which seems very unlikely. The real issue is for mothers giving birth now and the prospects for their children. I believe based on current evidence the mitochondrial donation is a very viable option for families with mtDNA disease.