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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Ethics

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Mitochondrial donation

Thank you for allowing the BMA some additional time to consider the ethical questions posed in your consultation on mitochondrial donation. The papers and questions were discussed by the BMA's Medical Ethics Committee and a draft response circulated to other BMA committees for comment. The BMA's response is set out below.

1. Emerging techniques such as PNT (pronuclear transfer) and MST (maternal spindle transfer) 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?

It is important to distinguish here between 'selecting for' particular genes to meet parental preference and 'selecting out' unhealthy genes that will cause severe disability and possible early death. The BMA supports the use of nuclear transfer techniques to avoid severe mitochondrial diseases. By the nature of the technique, the donated mitochondria will be passed on to future generations through the female line. The only way to avoid this is to prevent the birth of female children (see below for comments on sex selection in association with mitochondrial transfer). It is important that there is ongoing research and audit to establish the safety of the technique for future generations but there is also a moral imperative to pursue this work, for the benefit of those for who would wish to use this option as their only chance to have a healthy child genetically related to both of them.

2. 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?

Under the Human Fertilisation and Embryology Act 1990 (as amended) both a) and b) would involve the use of human 'embryos' , although this is not the case in all countries. For some people, however, the

merging of the DNA from the parents to create an embryo with a unique genetic identity is morally significant. Those holding this view are likely to find a) morally preferable because of the higher moral status afforded to the embryo once this stage of development has been reached. Given, however, that the law permits research up to 14 days after fertilisation where it is 'necessary and desirable', and the BMA supports this position, the BMA does not consider this to be a relevant distinction in terms of developing policy for mitochondrial transfer.

It has also been suggested that it is morally significant that b) uses the same technology as would be used to clone an embryo, but the BMA has always argued that it is the *intention* to create genetically identical individuals that is problematic about human cloning, rather than the technology itself. This is not cloning and should not be considered as such.

In the context of stem cell research the BMA has argued that, if equivalent results could be obtained, it would be preferable not to use human embryos, but we have argued strongly that until there is evidence about which technique would be more effective, research on all fronts should continue at the same time. The BMA takes the same approach here, and believes that research into maternal spindle transfer, pronuclear transfer and nuclear transfer should all be pursued at this time. Furthermore, Regulations should not specify which techniques should be adopted. This should be left to the HFEA to regulate on the basis of the best available evidence at the time.

As far as we can ascertain nobody is suggesting (c) as an option for mitochondrial disease at the present time and so the BMA has not considered this option.

3. 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?

There comes a time with any new procedure or technique where it is used in treatment for the first time. It is the role of the HFEA to assess the evidence and to determine at what stage there is sufficient information available to justify making the shift to clinical practice. This will depend both on the evidence of safety and efficacy and on the balance of benefits and risks. The alternatives for these patients are either to remain childless, to use a donor egg or to risk conceiving a child with a serious disorder (and many of these women will already have had children who have died or had repeated miscarriages). Delaying a decision to progress this work is, in itself, an ethical issue and the BMA is pleased that this debate is taking place now.

It is important that patients are informed of the novel nature of the procedure, what is known and what is unknown and are helped to make an informed decision about whether to proceed. Initially this should be considered as an experimental procedure with additional monitoring. Proper follow up studies of children born following such techniques, both medical and psychological, will be important.

4. 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?

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

6. 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?

These questions raise similar issues and so will be answered together.

The child will be the child of the intended parents whose nuclear DNA is used to produce the embryo from which the child has developed. The donor of the mitochondrial DNA should **not** be considered in the same way as an egg donor since her contribution is to provide an energy source for the cells only. Although there is still much that is unknown about the role of mitochondrial DNA, the scientific consensus is that it does not have any influence on the characteristics of the child. The reason children born following donor conception require information about the donor is because the information relates to them, as a person, and the donor's genes have contributed to that person's physical appearance and personal characteristics. The same does not apply to donated mitochondrial DNA.

It is also important to recognise that we all have a significant genetic link to people other than our parents – grandparents, aunts, uncles etc.

Perhaps the most appropriate analogy is to blood or bone marrow donation. The fact of having a blood transfusion or bone-marrow transplant would not have any impact on the identity of the recipient and nor would there be any 'special relationship' between the donor and recipient. Arguably an individual who is transplanted with someone else's heart has a far greater link with the donor than a child born with donated mitochondrial DNA but we do not generally suggest this has any impact on the individual's personal identity or attach special significance to the relationship between the deceased donor and the recipient.

7. 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?

The BMA does not have a clear view on this and a range of opinions were voiced by those consulted which fall into the three groups set out below.

a) There is still much that is unknown about the role of mitochondria and so a sensible precaution, in the first instance, would be to select only male children in order to avoid the risk of problems for future generations.

b) It is not unreasonable for people to request the selection of male children in order to protect against any possible risk to future generations. Where that is the wish of those undergoing the treatment, it would be acceptable to comply.

c) People should not be able to choose to have only male embryos replaced because the selection is not being undertaken to avoid a serious condition in the child to be born from the treatment and would therefore not meet the current criteria for PGD.

8. 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?

The BMA believes that Regulations should be made once the ethical and regulatory issues have been explored permitting the HFEA to authorise the procedure when it considers there is sufficient information available to allow people to give informed consent. The HFEA should also ensure that the clinics providing the treatment have the necessary expertise and that information is provided to patients giving details of the novel nature of the procedure and the level of unknown risk.

9. 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?

The most serious ethical concern of not allowing this procedure is that women who are at risk of passing on a serious disease to their children will be denied the option of having their own healthy children. Any risks or concerns about permitting this treatment (once its safety and efficacy have been determined as far as possible) need to be balanced against the harms that would arise from denying women this option. Developments would continue in other countries and so not only would the UK lose its world-leader status in this area of research, but women who wish to use the treatment would be forced to go overseas.

10. 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?

As with other donation of tissue or cells a record should be kept so that the donor can be traced if necessary in the future. In line with the comments above, however, this should not be considered in the same way as egg donation. It would not, therefore, be appropriate for the data to be held on the HFEA's information register and nor should the mitochondrial donor have access to information about the resulting child (or the resulting children have access to information about the donors) as they would in the case of gamete donation.