HFEA Consultation questions

1. Permissibility of new techniques

Having read the information on this website about the two mitochondria replacement techniques, 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.

CMF strongly opposes the use of these two new techniques to, in effect, genetically engineer babies and introduce heritable changes through the germ line. This research is not primarily about preventing suffering because the birth of children with mitochondrial genetic diseases can already be prevented in a number of ways. All that these proposed new techniques of 'mitochondrial replacement' add is that the mother will be genetically related to her child (except for the mitochondria). This is insufficient reason to permit crossing over a crucial ethical line which will be impossible to reverse or hold firm. **Changes would be permanent and irreversible**.

Both of the proposed procedures pose serious health risks to any progeny created that would be difficult, if not impossible, to fully and safely understand and specify in advance. They may – ironically - be worse than those caused by mitochondrial diseases, which vary widely in severity. Additionally, safe and reliable alternatives such as adoption, or the donation of eggs by another woman (or even PGD) further undermine arguments that these techniques are aimed primarily at preventing severe suffering.

Mitochondrial DNA and nuclear DNA interact with each other consistently and in complex ways that are imperfectly understood. As we expand further in response to Q7, the proposed techniques are far from being proven to be either possible, effective or safe and would involve enormous risk, making this whole consultation premature. To carry out mitochondrial replacement would involve experimenting on, and manipulating, vulnerable future human beings who are unable to consent, despite the fact that they would be the ones bearing the results and burdens of such experimentation. **Changes would be highly risky and dangerous for the progeny.**

Will the children born be healthy, normal or be suffering from defects that are in fact worse than mitochondrial disease itself? Even if the process itself were successful the risks of genetic modification and any disorders would be passed down to future generations of children too, not solely the first generation.

Inherited disease caused by mitochondrial DNA is relatively rare, on average, only one child in 6500 is affected by a *serious* mitochondrial disease.[1] Women at risk of having an affected child have several other far less experimental options available to them. **The proposed procedures would be 'useful' in only a very small number of cases.**

Neither Maternal Spindle Transfer (MST) and Pro-nuclear transfer (PNT) should be permitted.

Whilst our concerns apply equally to both proposed methods, there are some ethical differences between the two.

MST creates embryos from the eggs and sperm of three people. PNT uses eggs or sperm

[1] Giles, C, 'Mitochondria', *Wellcome News,* Issue 70, Spring 2012, page 24.

from either three or four people, depending on whether the donor embryo is created using sperm from the commissioning couple or a donor, and necessitates the destruction of embryos in the process.

PNT is ethically of more concern because it is akin to human reproductive embryo cloning and it involves creating two, and destroying one embryo (at least – this of course does not account for the embryos damaged and destroyed by the research itself). PNT involves cloning from one embryo, using a second embryo, minus its own pronuclei, to provide the bulk of the cell, to create a third, 'clone' embryo. Generating embryos exclusively to be used as cytoplasmic donors disrespects nascent human life, and any child born from this particular technique is actually formed from the bodies of two embryos created and destroyed as 'building blocks' for him/her.

Even leaving aside concerns about the welfare of individual embryos, this is a strikingly uneconomical procedure if at least two embryos must always be destroyed in order to create one that is intended for transfer to a womb, and in reality probably many more than two would be destroyed due to inefficiency.

Considering and weighing the benefits of both of these proposed techniques for a very small number of parents who want a genetically related child, versus the significant risks to that child and the profoundly disturbing implications for the human community, we believe that the case for maintaining the current proscriptions on human germline modification is clear.

2. 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?

The consequences of modifying the human germ line would be socially and ethically disastrous for both the child created and his/her descendants. It would also be impossible to hold a line restricting its use for further genetic alterations of human beings, with unforeseen consequences.

Over 60 countries prohibit human germ line engineering because of its profound social, ethical and unpredictable consequences for future generations. Scientists in countries that have not yet adopted public policies on human germ line modification have nevertheless observed the prohibition. In Europe nearly all countries except Britain have signed the Council of Europe Convention on Biomedicine and Human Rights which prohibits, under Article 13, interventions and modifications of the human genome. This underlines the seriousness of the ban.

As we have noted earlier, mitochondrial DNA and nuclear DNA interact with each other consistently and in complex ways that are imperfectly understood, thus the **health risks** to any future children, and their children, created by modifying the germ line would be of great concern.

Moreover, genetically modifying a human person turns that human into a **designed product**, **modifiable at will and without consent**. Humans should be respected and accepted as equals not selected and designed (or improved) to fit another's whim or will.

Once this is done for mitochondrial disease it will be **impossible to hold a line** to prevent germ line intervention (and engineering) being carried out for other diseases, for other reasons, and for less serious disorders. To start with, families with mitochondrial conditions caused by nuclear genes will argue that it is unfair to deny them the similar (predicted) benefits of genetic modification.

After that, there will be requests for genetic modification for traits other than mitochondrial disease. Where would we draw the line? We must not cross the line - currently held worldwide - represented by human germ line modification. Permitting this in the UK would

create a very serious precedent worldwide for the genetic engineering of babies.

3. 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?

Headlines along the lines of 'three-parent embryos' and 'three-parent babies' may not appeal to scientists, but they are biologically accurate. We may not know exactly *how* the mitochondrial DNA will be associated with a person's identity but we *do* know there will be three adults with whom it shares a genetic connection. All the participants in the process of brining the child into existence will be, to varying degrees, a parent.

Therefore we have to be concerned about the damaging, confusing psychological effect on any child from the fact that their DNA is derived from three or more separate 'parents'.

Claims that the genetic impact of inheriting a third person's mitochondrial DNA would be as minimal as 'changing the batteries in a camera'[2] are only based on current understanding. In reality our understanding of the amount, influence and purpose of mitochondria is still limited and conclusions such as this need to be treated with caution.

Ironically, claims that the mitochondria have little or no effect on a person's identity is in part undermined by the fact that they can have a very profound effect on a person's health and well-being – hence the whole purpose behind this research!

We do however have increasing anecdotal evidence about the importance of genetic heritage and parental bonds for those born from donated gametes and their desire to know about their full genetic heritage.[3] Some have described anger at feeling like a medical experiment and cited problems with understanding identity for themselves and their own children.[4]

Concerns about the long-term psychological effects on children born of experimental techniques should take highest priority. It is usually not until early adulthood, marriage, having children etc that people really begin to question and value their genetic heritage. It is at this time of life that many adopted children and donor-conceived adults question their biological background and parental bonds. As yet, there is little empirical research on the long-term effects on children born from donated gametes. The researcher, Susan Golombok acknowledges that few studies have included children at adolescence or beyond and little is known about the perspective of the individuals concerned. Moreover, her own samples are small and the children are mostly ignorant of their origins.[5]

Unfortunately, there is a tendency to give more attention to the 'rights' (self-interest?) of adults to assisted reproduction rather than to the best interests of the children born. Yet the warnings from anecdotal testimonies about the damage that the manipulation of genetic heritage, parental bonds, identity and self-understanding can have in the long-term should be heeded. There is, at the very least, a need to carry out more research on parental bonds and belonging for adults born of donated gametes.

Although MST tries to erase the identity of the egg donor mother, the egg will still bear traces of her identity and the child will be able to trace some of her maternal ancestry through her.

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[2] http://www.telegraph.co.uk/science/science-news/9025121/Babies-with-three-parents-possible-within-three-years.html

[3] Note the court case by Joanna Rose in the UK. http://www.dailymail.co.uk/health/article-115840/Sperm-donor-children-launch-court-fight.html See also '*Who Am I? Experiences of donor conception'* Dr A McWhinnie. 2006.

[4] '*I wasn't the person I thought I was*!' Inside Story DVD, www.concordmedia.org.uk

[5] http://www.centreforsocialjustice.org.uk/client/downloads/FathersNotIncluded.pdf

With PNT, the direct parents of any child created will actually be two (destroyed) embryos. In PNT there will be up to four parents involved in the conceiving of the original two IVFembryos. Identity problems may therefore be more severe, and certainly unpredictable, as the child will be a clone formed from 'spare parts' of two deliberately destroyed embryos.

However this issue is not solely about issues of identity. It is also about reconstructing individuals, about the mixing and matching of genes and the breaking down of the natural boundaries and barriers in order to design and build new bodies. The public understands the similarities with the genetic modification of crops and we believe that this is part of the cause of public unease and concern. These are concerns that we concur with.

4. The status of the mitochondria donor

a) 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.

This situation can be distinguished from existing types of donation which are used to directly save the lives of patients (such as blood and organ donation).

Sir Mark Walport, in an article in *The Times* argued that: '*Medical procedures that introduce a donor's biological material into the body are … long accepted. If a child with donated mitochondria can be said to have three parents, then the recipient of a heart transplant could be said to have four.*'[6]

However, this is disingenuous. Neither MST nor PNT can be compared to heart transplants, nor to bodily structural repairs, as they do not involve genetic transfer, nor are inheritable and thus do not generate ethical and personal questions regarding identity.

There has been little public concern voiced about the donation and acquisition of sufficient numbers of eggs from women for these procedures, particularly MST. Large numbers of women's eggs will be required to generate embryos 'free' of unhealthy mitochondria. We would like to know how many eggs the Newcastle team have already required to date to generate embryos via PNT – some have been used in the project but it is far from clear how many have been used, and little has been publicly said about the actual amount needed to progress this research and 'treatment'.

Egg donation – an important aspect of this proposed research - raises significant ethical and safety concerns. Women are being offered inducements to 'donate' their eggs, with cut price IVF treatment. This is offered alongside promises of potential 'cures' for diseases. This encourages vulnerable women undergoing IVF treatment, and other potential providers of eggs for research, to take known and unknown health risks for unethical research. In our view, encouraging healthy women to risk damage to their own health by providing 'spare' eggs for unethical treatment for others is not medically, ethically or socially justifiable.

b) Thinking about your response to 4a, what information about the mitochondria donor do you think a child should have? (Choose one response only)

Please explain your choice.

- The child should get no information

[6] http://www.thetimes.co.uk/tto/opinion/columnists/article3292262.ece

- The child should be able to get medical and personal information about the mitochondria donor, but never know their identity
- 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
- Other
- I do not think mitochondria replacement should be permitted in treatment at all

MST and PNT should not be permitted. However if MST were to be legalised and children born, such children should not be deprived of knowledge of the egg donor mother. They should have similar rights to other children conceived using donor eggs or sperm.

In PNT there will be up to four parents involved in the conceiving of the original two embryos. The PNT child will then be a clone made from these two embryos, which are destroyed in the process. The mitochondrial DNA will come from the egg donor, via the second, donor embryo.

With such 'parental' confusion, any child born from this procedure should, at very least, be offered full knowledge of the woman who donated the second egg and of the man whose sperm was used to create the donor embryo with that second egg (if this man is different from the child's social father).

A problem with this consultation structure is that by only allowing one box to check, there is no opportunity for those opposed to express a view about how to mitigate the bad effects.

5. 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)

- Clinics and their patients should decide when mitochondria replacement is appropriate in individual cases
- 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
- 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
- I do not think mitochondria replacement should be permitted in treatment at all

Please explain your choice.

MST and PNT should not be permitted.

As we noted above, by only allowing one box to check, the consultation does not allow those opposed to these techniques adequately to express a view about how to mitigate the damaging effects.

We recommend that clinics and patients should not have regulatory oversight.

Unfortunately, it is unlikely that if such techniques are legalised, any regulator would be effective in safeguarding against ever-expanding use of the techniques. A preferable safeguard would be to use Parliament to set and maintain clear rules as to which techniques are prohibited and to ensure these are held.

6. Should the law be changed?

In Question 1, we asked for your views on these techniques. 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? You may wish to address the two techniques separately.

For reasons stated earlier, MST and PNT should not be permitted and regulations should not be created to allow them in the UK.

Inherited disease caused by mitochondrial DNA is relatively rare, affecting on average, only one child in 6,500 with a *serious* mitochondrial disease.[7] Women at risk of having an affected child have other options available to them, so these extreme procedures would be considered only in a very small number of cases. The desire to have a (mostly) genetically related child, in so few cases, does not justify cloning, embryo destruction and, most concerning of all, genetically modifying children by altering their germ line.

A decision to begin human germ line modification should not be made by a single maverick country alone. **There should be a formal international moratorium on any procedures involving human germ line modification**.

PNT is ethically more concerning than MST so if the government is determined to permit mitochondrial replacement - which we believe would be a serious error - it would be preferable to only permit MST. Even with this restriction however, we reiterate our earlier warning that once the process is started, it will be difficult to prevent it from being used for other disorders.

Initially there will be pressure to allow genetic modification to treat conditions caused by mutations in nuclear genes. Proponents will argue that since the line has been crossed already, it would be illogical and unfair to families affected by mitochondrial conditions caused by nuclear mutations not to receive the same benefits as those whose conditions are caused by mitochondrial mutations. Where will the boundaries be drawn after this?

The fundamental problem is that once we have judged some disabled babies not worthy of being conceived, there is no real justification to then prevent the conception and birth of others.

We should be concentrating on finding alternative treatments for disabling conditions, not preventing those who suffer from them from being born or conceived. Already there has been

[7] Giles, C, 'Mitochondria', *Wellcome News,* Issue 70, Spring 2012, page 24.

some progress in seeking to repair faulty mitochondria[8] which should be funded and developed instead of considering MST and PNT.

7. Further considerations

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

These proposals and the drive for this research appears to be driven by the same centre that brought us cloning and animal-human hybrids – now both farcical footnotes in history. There can be a tendency for scientists to be driven more by cutting edge research than actual medical need and therapies. If medical need were at the forefront, why not invest the same millions into actual treatments (such as repairing faulty mitochondria[9]) that could also benefit those already born, or who will be born, rather than preventing some from being born?

Decision makers should seriously question the premise of the actual research. We have significant reservations about both the effectiveness and safety of these techniques.

As the powerhouses of cells, the correct assembly of mitochondria is vital for power to be generated, a process that relies on numerous interactions between nuclear DNA and mtDNA. Transplanting a nucleus from one mitochondrial background into that of another during pronuclear transfer (PNT) or maternal spindle transfer (MST) may result in nuclear-mitochondrial incompatibility, unhealthy mitochondria and symptoms reminiscent of mitochondrial disease, in any 'mitochondrial replacement' babies produced.

Nuclear-mitochondrial compatibility is essential for nuclear transfer. However individual humans are characterised by a complex mixture of related mitochondrial genotypes rather than a single genotype, which suggests that the application of this technology may be more unpredictable, complex and limited (to certain combinations of haplogroups) than is being suggested.[10]

There are numerous somatic and embryonic cell nuclear transfer animal studies that show **mtDNA carry-over from the original cells to embryos, foetuses and offspring is a regular phenomenon**. mtDNA carry-over has been detected in 165 out of 204 (54 %) cases, with up to 59% mtDNA carry-over reported in one offspring.[11] Importantly, this amount was more than the amount present immediately after the somatic cell nuclear transfer, thus the authors suggested the mtDNA of the original somatic cell had been **amplified** during development.

Clearly not all studies have found high mtDNA carry-over. The Nature 2009 report on the birth of non-human primates[12] showed undetectable levels of spindle donor mtDNA, but there are **sufficient studies showing carry-over** for the effectiveness of this technique to be questioned, along with concerns for the **outcomes when this is 'tested' out on humans**.

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[8] *e! Science News,* 13 March 2012, see http:// esciencenews.com/articles/2012/03/13/ correcting.human.mitochondrial.mutations, as at 14 November 2012

[9] *e! Science News,* 13 March 2012, see http:// esciencenews.com/articles/2012/03/13/ correcting.human.mitochondrial.mutations, as at 14 November 2012

[10] See the non-confidential evidence to Mitochondria Review, HFEA, 2011.

[11] Takeda, K., S. Akagi, et al. (2003). "Proliferation of donor mitochondrial DNA in nuclear transfer calves (Bos taurus) derived from cumulus cells." Mol Reprod Dev 64(4): 429-37.

[12] Tachibana et al, Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature 2009;461;367-72

There is a therefore a high possibility that, despite best efforts, the unhealthy mitochondria will be carried over and amplified to levels that could cause mitochondrial disease in 'mitochondrial-replacement' babies.

This proposed research is <u>not</u> about treating mitochondrial disorders - which we would support.

Instead it is primarily about trying to prevent people being born, or at least helping a very small number of mothers who carry the gene to have their own genetically (except the mtDNA) related children who are unaffected.

Whilst we appreciate that parents prefer to be the nuclear genetic parents of their children, an absolute insistence upon this is unreasonable in view of the profound ethical and safety concerns with it.

Neither MST nor PNT would be safer or more efficient than standard egg donation, nor would they do any more than standard egg donation to prevent the transmission of mitochondrial disease, nor would they avoid the need for an egg donor (an egg mother, in the case of MST). The aim of MST and PNT is to satisfy the wish for a (mostly) genetically related child, which does not justify cloning, embryo destruction, genetically modifying children and altering the germ line.

In conclusion, there are already solutions available for those couples who find themselves in the tragic position of carrying genes for mitochondrial disease – including adoption and egg donation (although we have serious ethical reservations about the latter) - rather than these dehumanising, risky and highly experimental options that will cross a rubicon into germ line engineering.