



Medical frontiers: Debating mitochondria replacement

Annex I: Summary of evidence

Report to HFEA

February 2013

OPM
252B Gray's Inn Road,
London WC1X 8XG

tel: 0845 055 3900
fax: 0845 055 1700
email: info@opm.co.uk
web: www.opm.co.uk

Client	HFEA
Document title	Medical frontiers: Debating mitochondria replacement summary of evidence
Date modified	12 March 2013
Status	Final
OPM project code	8984
Author	Robin Clarke, Remco van der Stoep
Quality assurance by	Diane Beddoes
Contact details	
Main point of contact	Tim Vanson
Telephone	020 7239 7806
Email	tvanson@opm.co.uk

If you would like a large text version of this document, please contact us.



Contents

1. Introduction	1
1.2 Methodological statement	2
2. Public dialogue and consultation findings	5
2.1 Permissibility of new techniques	5
2.2 Changing the germline	9
2.3 Implications for identity	11
2.4 The status of the mitochondria donor	14
2.5 Regulation of mitochondria replacement	17
2.6 Attitudes to legislation change	19

1. Introduction

Mitochondria are present in almost all human cells. They are often referred to as the cell's 'batteries' as they generate the majority of a cell's energy supply. For any cell to work properly, the mitochondria need to be healthy. Unhealthy mitochondria can cause genetic disorders known as mitochondrial disease.

There are many different conditions that are linked to mitochondrial disease. They can range from mild to severe or life threatening, and can have devastating effects on the families that carry them. Currently there is no known cure and treatment options are limited. For many patients with mitochondrial disease preventing the transmission of the disease to their children is a key concern.

Mitochondrial disease can be caused by faults in the genes within a cell's nucleus that are required for mitochondrial function or by faults within the small amount of DNA that exists within the mitochondria themselves. It is the latter form of mitochondrial disease that could be avoided using two new medical techniques, termed pro-nuclear transfer (PNT)¹ and maternal spindle transfer (MST)² which UK researchers are working on.

These techniques are at the cutting edge, both of science and ethics and are currently only permitted in research. They involve removing the nuclear DNA from an egg or embryo with unhealthy mitochondria, and transferring it into an enucleated donor egg or embryo with healthy mitochondria.

The Human Fertilisation and Embryology Act (1990) (as amended) ('the Act') governs research and treatment involving human embryos and related clinical practices in the UK. The Act currently prevents the clinical use of these techniques (or any other technique that involves genetic modification of gametes and embryos to treat patients). However, in 2008 the Act was amended, introducing new powers which enable the Secretary of State for Health to permit techniques which prevent the transmission of serious mitochondrial disease. The Secretary of State for Health and the Secretary of State for Business, Innovation and Skills asked the Human Fertilisation and Embryology Authority (HFEA) to seek public views on these emerging techniques. On considering advice from the HFEA the Government will decide whether to propose regulations legalising one or both of the procedures for treatment.

The HFEA, together with the Sciencewise Expert Resource Centre³, therefore commissioned OPM (in partnership with Forster and Dialogue by Design) to conduct a multi-method research and engagement project looking at the possible social and ethical issues and arguments relating to the techniques. The project consisted of five strands:

¹ Pronuclear transfer involves transferring the pronuclei from an embryo with unhealthy mitochondria and placing them into a donor embryo, which contains healthy mitochondria and has had its pronuclei removed. A pronucleus is a small round structure containing nuclear DNA seen within an embryo following fertilisation. A normal embryo should contain two pronuclei, one from the egg (maternal pronucleus) and one from the sperm (paternal pronucleus).

² The maternal spindle is a structure within the egg containing the mother's nuclear DNA. Maternal spindle transfer involves transferring the spindle from the intending mother's egg, with unhealthy mitochondria, and placing it into a donor egg with healthy mitochondria.

³ The Sciencewise Expert Resource Centre (Sciencewise-ERC) is the UK's national centre for public dialogue in policy making involving science and technology issues

1. Deliberative public workshops
2. Public representative survey
3. Patient focus group
4. Open consultation meetings
5. Open consultation questionnaire

This research provides the evidence base that will inform the HFEA's advice to the Secretary of State.

This report provides an overall summary of the evidence from the five different consultation strands and, where possible, highlights areas of agreement and disagreement. It sits alongside the five separate strand reports.

1.2 Methodological statement

The five separate strands summarised in this report were:

- **Deliberative public workshops:** Workshops were held in Newcastle, Cardiff and London in July 2012 and participants met twice in each location. Participants were recruited to represent a broad spectrum of age, gender, socio-economic status and family circumstances. Thirty people were recruited for each location. The aim of this strand of the consultation was to explore public attitudes in-depth, and to understand participant viewpoints as they become increasingly engaged with, and knowledgeable about, mitochondrial disease and mitochondria replacement techniques. The first meetings focused on helping participants to understand the potential treatment techniques – pronuclear transfer (PNT) and maternal spindle transfer (MST) – while the second events focused on the potential social and ethical issues relating to the techniques.
- **Public representative survey:** In August, just under 1,000 face-to-face interviews were carried out with members of the public across 175 random locations. For each location, demographic quotas were set to ensure the sample was representative. The aim of the survey was to benchmark public opinion on: general attitudes towards medical research and genetic treatments; awareness of IVF and mitochondrial disease; views on the genetic treatment of mitochondrial disease; and attitudes to the regulation of genetic treatments.
- **Open consultation meetings:** Two public meetings were held in November 2012. The first of these was in London (53 attendees) and the second in Manchester (39 attendees). The meetings were open to anyone wishing to attend and were advertised on the HFEA consultation website, through HFEA networks, and promoted to stakeholders and the public in a number of ways. At each meeting, a panel of speakers shared their knowledge and views with audience members. Panellists were selected to reflect a range of different perspectives and areas of expertise, and to provoke discussion amongst participants. The events involved a combination of small group discussions around particular issues, whole group debates, and discussion between and across the panel and the floor.
- **Patient focus group:** One focus group was held with six participants. The aim of the focus group was to create a forum where people affected by mitochondrial disease, either directly or indirectly, could give their in-depth views on mitochondria replacement techniques. The group was comprised mainly of parents who had children affected by

mitochondrial disease and someone who had been diagnosed with MELAS⁴. One telephone interview was also carried out with someone unable to attend the focus group.

- **Open consultation questionnaire:** A public consultation was held between 17th September and 7th December 2012. Respondents were invited to consider a range of information presented on the consultation website, and to respond to seven questions using the online questionnaire. Responses made via email or post were also accepted while the consultation was open. A total of 1,836 responses were received, the majority of which were received via the consultation website. Respondents include stakeholder organisations, individuals with personal experience of mitochondrial disease as well as a large number of members of the public.

When reading this report the reader should keep in mind that the participants involved in each strand of the public dialogue had varying levels of knowledge about mitochondrial diseases and the associated concepts that were discussed. Some had little prior knowledge whilst others were well informed. The findings from the public representative survey should be treated as a snapshot of current public awareness of the issues and their views on them. People who completed the open consultation questionnaire formed a self-selected sample, rather than being recruited to a quota sample specification. This tends to mean that their levels of awareness and knowledge of the issues consulted on were higher than those of the population as a whole, though this cannot be assumed to be the case for all consultation respondents. The same point can be made about those attending the open consultation meetings. Patient focus group participants were directly or indirectly affected by mitochondrial disease and hence were likely to have higher levels of awareness and knowledge. Participants in the deliberative public workshops went on a journey from initially low levels of awareness and knowledge to develop a deeper understanding of the science and social and ethical issues. Deliberative public dialogue aims in part to explore whether and how information and deliberation impacts on participants' views. They were provided with information about the subject by experts, videos and information sheets.

A further point to bear in mind when reading this report is that many of those with higher levels of knowledge and awareness of the science and wider debate surrounding it have well considered and firmly held views about the issues.

⁴ Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes – abbreviated to MELAS.

The table below provides a summary of the types of people that took part in the consultation, how many participated, how they were selected and what their level of knowledge about the subject matter is.

Table 1: Summary of participants in the consultation

	Participants	Selection method	Knowledge level of consultation issues	Number of participants
Deliberative public workshops	Members of the public	Recruited to a quota sample	Low at start of the workshops, much higher by the end	Approx 30 participants at each workshop
Public representative survey	Members of the public	Random quota sample	Most people likely to have had low knowledge of the consultation issues	979 participants
Open consultation meetings	Interested stakeholders and members of the public	Self-selected sample through open invitation	Interested and knowledgeable about the consultation issues, but levels of knowledge were likely to be variable	53 participants (London meeting) and 39 participants (Manchester meeting)
Patient focus group	People directly or indirectly affected by mitochondrial disease	Invited to attend through patient contacts and patient groups	Interested and knowledgeable about the consultation issues, but levels of knowledge were variable	7 participants (including 1 telephone interview)
Open consultation questionnaire	Interested stakeholder and members of the public	Self-selected sample	Varied - relevant information was available via the consultation website which respondents were encouraged but not obliged to consult	1,836 participants responded to the consultation

2. Public dialogue and consultation findings

The headline findings of all five strands of the public dialogue and consultation fall under six main themes:

1. Permissibility of new techniques
2. Changing the germline
3. Implications for identity
4. The status of the mitochondria donor
5. Regulation of mitochondria replacement
6. Attitudes towards legislation

Under each of these headings we set out the main findings from each consultation strand, highlighting areas of agreement and disagreement. Where possible, findings were analysed across the different strands to identify areas of consensus and difference.

This report does not comment on the accuracy of people's views about the issues covered by the consultation. It does not seek to endorse or reject people's views; it presents them in an objective manner for the reader to consider.

2.1 Permissibility of new techniques

Deliberative public workshops

At the first deliberative public workshop meetings in Newcastle, Cardiff and London the focus was on providing participants with information on the science behind the new mitochondria replacement techniques. Overall, participants were fairly positive about the techniques, seeing them as a way of offering parents the chance to have a healthy child that is genetically their own. A minority argued against the use of pronuclear transfer (PNT) because it involves manipulating and disposing embryos. This argument tended to be made in terms of 'other people' finding the use of embryos in PNT an issue, they felt that it would be 'religious groups' who were the most likely to object. Some participants suggested that the use of these techniques might be seen as "*playing God*" and could result in a "*slippery slope*" to "*designer babies*" and "*aborting disabled people*." Others raised concerns about the safety of the new techniques, and wanted to know about the risks involved and whether research has been carried out in terms of success rates and long-term safety.

In this first round of deliberative public workshops, participants held largely positive views that were shaped by two main factors. Firstly, comparisons were made between the new techniques and treatments that are currently available, such as pre-implantation genetic diagnosis (PGD)⁵ and prenatal diagnosis (PND)⁶. Consequently, participants felt that the new

⁵ This is a procedure that involves testing an embryo in the laboratory for a genetic disease.

⁶ This term describes any technique used to determine whether a developing fetus is affected with a genetic disorder or abnormality. This may involve testing the blood taken from the placenta, using ultrasound scanning or retrieving amniotic fluid for testing.

techniques offered a better outcome because they allow parents to have a healthy child that is genetically *'their own'*. The second factor was the importance they placed on personal and individual choice. Participants did not think it was appropriate to prevent access to these new techniques to individuals and families simply because some people (and groups) are opposed to their clinical use.

Public representative survey

In the public representative survey, participants were asked for their initial reactions to different aspects of potential treatments for mitochondrial disease. The first question was:

'Scientists are developing techniques which could remove the chance of these mitochondrial diseases by altering the genetic make-up of an egg or embryo during IVF. What is your initial reaction to this?'

Over half (56%) were *'very'* or *'fairly'* positive about this and 10% were *'very'* or *'fairly'* negative about this. One third (33%) of respondents were undecided (*'neither positive nor negative'* or *'unsure'*).

To help understand survey respondents' views (in this and later sections of this report) about techniques to avoid mitochondrial diseases participants were asked more general questions about attitudes towards medical research, genetic treatments and existing IVF treatments. The findings showed that people were very positive about the benefits of medical research. Nine out of ten agreed that it *'can do a lot to reduce human suffering'* and it *'creates knowledge and treatments which will benefit the wider healthcare system'*. However, 50% also felt that *'the application of medical research leads to unforeseen negative side effects'* with 15% disagreeing and just over a third (36%) saying they were unsure.

Attitudes towards the treatment of people with genetic diseases were very positive. Almost nine out of ten (88%) members of the public were in favour of providing people with serious genetic diseases with *'healthcare and treatment to help manage their condition'* and nearly three-quarters (74%) felt that *'families at risk of having a child with a serious genetic disease should be able to avoid that risk through genetic testing.'* The question about genetic treatment received slightly more opposition (7%) as well as uncertainty (20%).

Respondents showed a high level of awareness of IVF, with 86% saying they had heard of it compared to 14% who had not. Awareness in London was lower than in other areas (65%), which may have been a result of particularly low awareness among BME groups and some faith communities; for example, 51% amongst Muslims. Awareness of mitochondrial disease was relatively low across all respondents, with just over a quarter (28%) stating that they had heard of the disease. Awareness was strongly correlated to levels of education, which rose from 10% (low levels) to 25% (medium levels) and 46% (high levels)⁷. There were small variations by faith: 34% of those with no religion saying they had heard of mitochondrial disease compared to 26% of Christians and 22% of Muslims.

When people were asked about their attitude to the testing of embryos during IVF, nearly two-thirds (65%) were *'very'* or *'fairly'* positive and 27% were undecided or unsure. There

⁷ In the representative survey respondents were asked to indicate their highest level of education-related qualification—low levels: no qualifications; medium levels: O-Level, GCSE, A-level, GNVQ or similar; high levels: a degree, postgraduate, NVQ/SVQ level 4 or HNVQ.

was a drop off in positive ratings for some of those who described themselves as Christians and slightly more so for Muslims.

Open consultation meetings

At the open consultation meetings there was a marked difference in the overall balance of views. Greater support for mitochondria replacement was seen in Manchester than in London where those opposed or concerned about the techniques were more vocal (although they were not the majority). When noting this difference it is important to reflect on the composition of attendees. London was attended by some firm sceptics and stakeholder groups who focussed on the risks and uncertainties attached to the new techniques. As a result, the debate at this meeting focussed on the moral status of the embryo and comparisons were made to cloning. By contrast, the Manchester meeting was represented by students and patients who were distinctly more supportive of the techniques with participants arguing that potential social or ethical issues were not significant enough and should not prevent the clinical use of the techniques to help others.

A few participants at the London event voiced concern about possible unforeseen effects of the new techniques and made comments that included: *“we are playing with something unknown and the full risks need to be understood.”* Another statement of concern was the danger of *“taking human embryos lightly.”* Terms such as *“unnatural”* and *“violating the integrity of nature”* were also used. However, the majority of attendees were more positive about the techniques and less worried about risks.

During the debate session at the event in London, some participants suggested that the HFEA needs to consider the *“important moral differences between the two techniques.”* The implicit suggestion was that PNT, which relies on the creation of embryos that will never be transferred into a woman, is more ethically objectionable than maternal spindle transfer (MST). Participants at the Manchester meeting showed a greater consensus about the permissibility of both techniques.

The issue of safety was discussed for some time in Manchester. When a panel member questioned the safety, an audience member responded by saying, *“of course there are risks...this is what happened with the first organ transplant. This is what happened with the first egg donation. More information should be found, more research should be done, but this doesn’t mean it shouldn’t move forward.”* This quote is reflective of how the vast majority of attendees at the Manchester meeting felt. While at the London public meeting there were some people who were critical of the new techniques, in Manchester it was clear that participants were much more positive about them.

Patient focus group

The patient focus group participants were extremely positive about the new techniques. In part this was because unlike current options they could prevent the resulting child, and also their children from having mitochondrial disease: *“anything that could eliminate mitochondrial disease is a wonderful thing...”* One person did point out that while the techniques are not a cure, they are the best option currently available. Participants were also generally positive about mitochondria replacement because it could enable parents to have a child which is genetically their own, *“it will still be the genes of the mother and father, the child will still look and sound and act like its parents, that’s really important.”*

Some participants did want clarification on the safety and risks of the techniques. One person had questions about what needed to happen to refine the techniques and how

confident the scientists are that the technique would work. She had concerns that the first babies born from these techniques would be an “*experiment*”: “*Imagine being the parents of that first child born this way...it doesn't sit right with me.*” Others disagreed with this, saying they would be happy to be the first, “*it is a risk I am willing to take...for me the risk is lower than the risk of the disease.*” Some participants said that there is always a degree of uncertainty with respect to medical innovation and that this is “*a part of medical progress.*” Participants stressed the importance of individual parents and families having the choice about whether or not to use these new techniques, arguing that wider social concerns should not be allowed to prevent them from making this choice.

Open consultation questionnaire

The first question of the open consultation questionnaire asked respondents for their views on offering MST and PNT to people at risk of passing on mitochondrial disease to their child. A total of 1,235 respondents answered this question, of which slightly more disagreed with the introduction of both techniques. Looking at respondent types, there was a difference between the views expressed by respondents in specified categories, such as ‘student’ and ‘family member or friend affected by mitochondrial disease’, who were more often in support than in opposition, and those by respondents describing themselves as ‘other’, who predominantly stated opposition.

Proponents of the techniques tended to focus on the benefits they could offer to intending parents, children, or society more broadly, particularly the potential to avoid disease and allowing parents the opportunity to have a healthy child: “*If by introducing both these techniques, we can wipe out mitochondrial diseases and the suffering that goes with it, then it can only be a good thing.*” Some felt that if the techniques are possible, there was an ethical obligation to implement them.

In contrast, those opposing the techniques were more likely to discuss ethical issues, often arguing that the use of the techniques would amount to inappropriate interference with the natural or spiritual aspect of reproduction: “*It is not imperative that people have their own biological children, in fact such conditions are nature's way of preventing weaknesses being passed from generation to generation.*” Others focused on the use of embryos, particularly in relation to PNT, arguing that any artificial or *in vitro* manipulation of embryos is unethical. Where respondents support one technique in particular, they tend to prefer MST because this technique replaces mitochondria in eggs rather than embryos.

Comments about the permissibility of the techniques were also prevalent in responses, received in different formats, which did not respond directly to the questions asked in the online questionnaire. A few of those expressed support, but many more (some 275 in all – most using very similar wording) say they believed the techniques were unacceptable.

Summary

It is clear that most people believe the two new techniques offer the potential of significant improvements on the reproductive options currently available for women with unhealthy mitochondria. Across the different dialogue strands, most participants seemed to be positive about the techniques with the exception of the open consultation questionnaire where more respondents were opposed than supportive. It was also particularly noticeable that for the majority of people coming to this topic for the first time (mainly people taking part in the deliberative public workshops and the public representative survey), the potential benefits of the new techniques outweighed their concerns about the potential risks. Amongst these

newcomers to the topic, a substantial proportion was undecided and only a few had an initial reaction of disagreeing with the use of these techniques. It is not possible to say whether those who were undecided would become supportive or unsupportive of the techniques if they were given more time to think about and discuss them. It was noticeable that some of them wanted more information about the safety of the techniques before deciding one way or the other.

Those already familiar with the techniques, and the social and ethical debates around them, tended to have set views on whether they should be permitted or not. The majority who took part in the open consultation meetings and the patient focus group were in favour, but at the former there was some very vocal opposition.

2.2 Changing the germline

Deliberative public workshops

'Changing the germline' refers to the fact that any changes to a person's mitochondria will be passed down the maternal line through the mitochondrial DNA to the next generation, and if the child is female, to the child after that and so on. People taking part in the deliberative public workshops were presented with information and evidence on what is currently known about the risks and uncertainty of changing the germline. The majority of these people felt that the benefits that would follow from using the new techniques outweigh those risks. Furthermore the risks were not seen as of sufficient magnitude to warrant disallowing techniques that would enable parents to have a healthy child. Some participants pointed out that the introduction of any new treatment will involve some degree of uncertainty. Analysis of the ethics questionnaires show that throughout their discussions about changing the germline, participants' attitudes remained stable, with 64% saying they were *'not at all'* or *'not very'* concerned prior to the discussion and 62% at the end⁸.

Participants' views about the acceptability or not of changing the germline were largely shaped by the importance they placed on individual and personal choice for parents.

Public representative survey

In the public representative survey participants were asked about their attitude to changing the germ line, assuming this was shown to be safe. Just over half (52%) said they were *'very'* or *'fairly'* positive about it, 12% were *'very'* or *'fairly'* negative about it, and 36% were *'unsure'*.

⁸ The ethics questionnaire was a brief survey which participants were asked to complete at the start of the meeting, before they received information about an ethical issue and discussed it with other participants. Participants were then asked to complete the questionnaire after receiving the information and having group discussions. The aim was to see if people's views changed as a result of receiving new information and when hearing the opinions of others.

Open consultation meetings

At the open consultation meetings there were three types of response to this issue. Some people felt that the germline would not be changed significantly. They argued that parents could 'ideally' choose a mitochondria donor with a mitochondrial DNA sequence that was very similar to the mother's. This view was supported by the statement that mitochondrial variation is limited, especially in individuals of the same ancestral origin (e.g. European or sub-Saharan African). A second general response was that the germline effect would be significant and negative. Those responding in this way felt that mitochondria replacement posed *"serious risks to societies and individuals."* The final response highlighted that the techniques would have a significant but positive effect on future generations. People who said this felt that it would be *"more irresponsible"* for society to allow families with a history of the disease *"to have more children and face the risk of more affected children being born."* Comments were made that this would be changing the germline *"for the better"* by creating a *"healthy cell"*, and that *"the child will go on to pass on healthy mitochondria and children will be free from mitochondria disease."*

During the public debate sessions in both London and Manchester, two audience members made a similar point in response to one panellist who argued that changing the germline is morally unacceptable and that it might be difficult for the child to come to terms with how they came into being. In London, the audience member said, *"as parents we are making decisions for our children all the time, some of which they may not agree with...as long as we did it in their best interest, fine. We can do no more than that"*, while in Manchester a participant voiced, *"I have no problem saying to my child 'because I love you'...and why this has this happened to you? So you could live a long, healthy, fulfilling life without the obstacles I've had to deal with."* These two quotes reflect the majority of participant views in London and almost all of those in Manchester.

Patient focus group

Participants in the patient focus group expressed very limited concern about changes to the female germline following the use of these techniques. They felt that a change in the germline would be 'preventing the disease' and that this is in essence a good thing: *"I have no problem with removing whatever has to be removed and changing the germline...I don't care."*

Focus group participants also said they were comfortable with parents making this decision on behalf of their children because it is about ensuring that their children are healthy. This was felt to be more important than changes to the germline. One participant felt that future generations may resent their parents for not having used a technique that could have saved them much pain and suffering.

Open consultation questionnaire

In the open consultation questionnaire, respondents were asked whether they thought there were social and ethical implications to changing the germline. Of the 1,115 respondents, those more in favour of the techniques argued that there were no implications, that the only implication was the reduction in instances of a terrible disease, or that any negative implications are out-weighed by the positives. The main theme running through responses was the uncertainty and risk involved in introducing a new technique. Many respondents expressed concern about the extent to which any consequences can be predicted: some respondents commented that *'scientific understanding of genetics is far from*

comprehensive'. Others argued that if negative implications are identified, the consequences (once introduced to the germline) would be so severe and far reaching that even a small risk should be considered carefully.

One concern raised relates to the way in which society would view those treated – or not treated – using the proposed techniques. Some respondents felt that if the techniques are made available there will be pressure on parents to use them, discrimination against those who chose not to, and possibly a knock-on effect on attitudes towards disabled people more generally. Others were concerned that those born as a result of the techniques might be treated differently because of it, though some discount this, arguing that *'the new technique(s) will become generally accepted, as new advances always are.'*

The predominant ethical issue raised was that making changes to the germline for this purpose could lead to other changes becoming more acceptable; many respondents identified the idea of germline change with controversial terms like eugenics and cloning. Others argued that any change to the germline is inappropriate because there is no way for all those affected to give consent; a view contradicted by a few who saw making choices for subsequent generations as a very ordinary part of being a parent.

Summary

The impact of mitochondria replacement techniques on the germline was one of the main ethical debates surrounding their use. Participants' views on whether this issue was deemed acceptable changed little during the deliberative public workshops. The prevailing view of a majority of participants across all five strands of the consultation was that the outcome of the techniques – a healthy child, free of faulty mitochondria and a potentially serious disease – outweighs the possible consequences of changing the germline, even though these might not be apparent until some time in the future.

As we learned in the permissibility discussion, most participants new to this topic felt that the known and unknown effects on the germline are acceptable; however, a substantial number remained undecided, neither for nor against the use of these new techniques.

Those more familiar with the new techniques tended to be familiar with the debate about germline effects and most discussing this issue did not change their existing views.

2.3 Implications for identity

Deliberative public workshops

Participants in the deliberative public workshops held varied views when discussing the potential implications of using DNA from three people on nature and sense of identity. Most participants rejected the 'three parent' label, arguing that mitochondrial DNA contributes little or nothing to a child's personal characteristics. However, a few participants felt that the donation of healthy mitochondria would have helped a child to exist free of mitochondrial disease and that this should be recognised by giving the donor some sort of parental status. Following group discussions, some participants who were at first against using DNA from three people voiced that their opinions had changed and this was not as serious an issue as they had been inclined to believe. Findings from the ethics questionnaires completed by participants showed levels of concern about this dropped slightly throughout the day: at the start of the day 51% said they were *'not very'* or *'not at all'* concerned about this issue whilst 57% said this at the end of the day.

Several factors affected the way in which participants formed and changed their views about mitochondrial donation. In all three deliberative public workshop locations, participants used a range of comparisons and analogies in their discussions, for example, adoption, organ donation and sperm donation. In their presentations, some experts made comparisons between mitochondria donation and blood transfusion or bone marrow donation, and the amount and role of mitochondrial donation in a person's genetic make-up was also highlighted.

Public representative survey

In the public representative survey, participants were asked about their attitudes to the eggs or embryos resulting from the new treatments containing small amounts of genetic information from a third person. Just over two fifths (44%) said they were 'very' or 'fairly' positive, 15% were 'very' or 'fairly' negative and 40% were 'unsure'.

Open consultation meetings

At the London open consultation meeting, most attendees were comfortable with the concept of a child having DNA from three people. They felt that mitochondrial DNA has little to do with "identity." One participant said: *"it's just like changing the battery in your laptop."* Another person said *"I don't think of my mitochondrial DNA in the same way as my nuclear DNA."* However, some participants suggested that as knowledge of genetics grows and develops, mitochondria might be found to play a greater role in determining personal characteristics than is currently assumed. During the debate session, views were polarised between those who felt mitochondrial DNA does not play a major role in a person's identity and those for whom the techniques result in an *"artificially constructed identity."*

When contrasting the new techniques with alternatives such as using a donor egg, participants in both London and Manchester felt that children born following mitochondria replacement may be *"happier"* in the knowledge that they are genetically related to both their parents. This comment introduced the possibility that mitochondria replacement techniques might actually resolve some identity issues.

At the Manchester meeting some participants suggested that identity is in part socially constructed and that the media can influence the ways in which people think about a person's identity. For example, *"sensationalised headlines"* surrounding mitochondria replacement techniques might have an impact on how children perceive themselves. Several participants attending the Manchester meeting referred to the position taken by the Nuffield Council of Bioethics on this issue⁹, which says that mitochondria replacement poses *"no ethical problems"* with regards to identity. Some explained their views by drawing comparisons between the new techniques and established medical procedures such as blood transfusions and organ transplants, neither of which are thought to have a significant impact on identity. One person made a counter argument to this by saying that mitochondria are present in every human cell.

One participant in Manchester, whose son is affected by a mitochondrial disorder, suggested that her child's mitochondrial DNA had helped shape his life, but had not affected who he is (e.g. how he looks). The implicit suggestion was that if he had healthy mitochondria, he

⁹ Nuffield Council on Bioethics, 'Novel techniques for the prevention of mitochondrial disorders: an ethical review' (2012).

would be exactly the same person but without having to cope with the debilitating effects of a disease.

There was more consensus in the public debate session of the Manchester meeting than there was in London. For example, an audience member in Manchester who made the following comment was not challenged by anyone: *"We are not changing characteristics, we are not changing those things that make you, 'you'. What we are changing is energy metabolism."*

Patient focus group

Participants in the patient focus group were aware that mitochondria replacement techniques mean that a child will have DNA from three people. They drew from their knowledge of the science to say that since no nuclear DNA would be used from a third party, the techniques are more akin to blood or tissue donation, therefore, a child's sense of self would be inherited from their parents: *"everything that makes you 'you' and that makes your child 'your child' is not touched."* Participants felt that some media reports on the issue have been sensationalist, resulting in public debate which is *"misleading"*, *"emotive"* and *"confusing."*

Open consultation questionnaire

Respondents to the open consultation questionnaire were asked whether they thought mitochondria replacement techniques have social or ethical implications relating to a person's sense of identity. Responses differed widely and were often influenced by a respondents' view on the status of the mitochondria donor; respondents who referred to the donor as a third parent usually expressed concern about implications for identity, whereas those who branded the social and/or genetic connection between donor and child as less significant mostly said they were not worried about implications for identity.

Among respondents who considered that these techniques are likely to have implications for a child's sense of identity, many felt that a child could be confused by knowing that they carry DNA from three people. Respondents believed this may saddle children with questions about who they are, and who their parents are, which they said will have detrimental impacts on their well-being. Some drew comparisons with adopted or donor-conceived children, arguing that they suffer from identity issues and that children resulting from mitochondria replacement could experience similar problems, or worse. A number of respondents felt that children born as a result of using PNT might also feel unhappy about the creation and destruction of embryos: *"Knowing that other people have to die (other embryos are destroyed) to give an individual life is an unfair burden to ask anyone to carry."*

Concerns about potential emotional or psychological damage experienced by children conceived with the help of mitochondria replacement were also expressed, often in similar wording, by many of those who took part without using the consultation website questionnaire - for example in a letter or email.

Respondents who thought these techniques have no implications for a child's sense of identity, or that these implications will be limited, often said that there is no connection between mitochondrial DNA and identity. They emphasised that the genetic information important for identity is held in the nuclear DNA and that this is not affected in MST and PNT, or that identity is determined by other than genetic factors: *"One's sense of identity is conditioned by many influences beyond the chance of genetic inheritance."* Some compared the mitochondria replacement with organ, bone marrow or blood donation, and highlighted that such procedures are not seen as influencing the recipient's sense of identity. Others saw

an analogy with sperm or egg donation, adding that the impact for the child will be similar, or less.

A relatively small number of respondents argued that mitochondria replacement is unlike any existing procedure, emphasising that identity implications are difficult to foresee, and that a cautious approach is important. Many others said that parents will be able to mitigate any identity implications by being open about how the child is conceived: *“I can imagine that if it is not explained clearly to either the parents or the children it could produce issues later in life”*.

Summary

Those participants who were less familiar with the consultation subject questioned what implications mitochondria replacement might have on a child’s sense of identity. This question raised slightly more concern than a change to the germline. For example, in the public representative survey those who agreed that it is acceptable for a child to carry a small amount of genetic information from a third person dipped just below 50%. The proportion of those who were undecided rose slightly to 40% and the negative figure also rose but remained low at 15%. This issue also raised slightly more concern at the deliberative public workshops, although some participants felt more comfortable about the issue once they had discussed it in further detail. The main reason for this concern was that some participants felt that a *“search for identity”* is something that all young people experience, and that there might also be an emotional impact on the child. Participants drew parallels with adopted children who are keen to find their biological parents as they seek to establish their identity.

Those who were more familiar with the techniques were also more familiar with this ethical issue. While most seemed to be comfortable with the idea of DNA from three people, others felt that this is not acceptable as our understanding of the role of mitochondrial DNA remains limited in some respects and we should be cautious about introducing these techniques into clinical practice.

2.4 The status of the mitochondria donor

Deliberative public workshops

Participants in the deliberative public workshops had varied views on whether a child born through the new techniques should be able to access information about the mitochondria donor involved. Those participants supporting donor anonymity felt quite strongly that the donor’s rights should be protected and that donors themselves should be given a choice about whether or not they want their identity to be revealed to the child. Others felt that a child should have the right to know the identity of their mitochondrial donor and access this information. At the end of the discussion, 45% of participants disagreed that any child born as a result of the new techniques should have the right to access information about the mitochondria donor, compared with 31% at the start of the discussion. The number of participants favouring the child’s right to know about their donor did not largely change – 33% at the start of the day to 31% at the end of the day.

Public representative survey

This issue was not discussed in the public representative survey.

Open consultation meetings

At the London open consultation meeting some participants emphasised the importance of keeping records of mitochondria donors, which linked to other comments about the newness of the science. Although there is currently no scientific indication that mitochondrial DNA has an influence on the characteristics of a person, participants noted that this area of genetic science is *“new and could change.”* Some participants argued that those willing to donate their mitochondria are choosing to be part of a child’s life and that we need to be *“upfront about what donor-ship means.”* Others highlighted that access to information about your origins is a fundamental human right. As such, any individual born following mitochondria replacement should be able to find out about their ‘third parent’ and their genetic origins in the same way those children of egg donors can. During the debate session at the meeting some participants called for the establishment of a mitochondria donor register.

In Manchester, participants expressed a range of views about the status of the mitochondria donor. While most were emphatic that there *“is no relationship”* between the child and the donor others maintained that donors are making a *“huge commitment.”* A number of people acknowledged that people may want to know the *“origin of their mitochondria”*, but the general view was that donors should be *“non-traceable.”* Some participants were concerned that the perception of donors as a *‘third parent’* could be strengthened if they could be traced and contacted.

Participants in Manchester described this as *“uncharted territory”* and felt that mitochondria donation could not be satisfactorily compared with either tissue or egg donation, and should be seen in a separate category of its own.

Patient focus group

People taking part in the patient focus group felt quite strongly that donors should remain anonymous. They also felt that donors should and would want to remain anonymous, because, unlike sperm or egg donation, no nuclear DNA is being donated: *“I’ve donated blood and haven’t given a second thought about where that’s going. There has never been a story in the press that someone wants to know where the blood came from that saved their life.”*

Open consultation questionnaire

Respondents to the open consultation questionnaire were asked how they view the status of a mitochondria donor compared to other, existing types of donor. A striking point made in responses was that for each type of donation, roughly equal numbers of respondents felt that mitochondrial donation is similar to another type of donation as those who see it as different (i.e. the number of respondents who saw donation of mitochondrial DNA as comparable to gamete donation was virtually equal to the number who saw it as distinctly different).

The most frequently made comparison was with gamete donation. Respondents argued that mitochondrial donation was similar to this because it involves procreation, or genetic transfer. Those who argued that mitochondrial donation is a different proposition often suggested that *“it won’t determine the characteristics of individuals it will simply prevent them from inheriting a genetic disease.”* Those who see mitochondria replacement as less significant than sperm or egg donation tended to support its introduction, whilst those who viewed it as equivalent to these forms of donation tended to be less in favour. There was a similar correlation between views on the contribution of the mitochondria to the resulting child and views on the role of

donor as a 'parent'; where respondents see the donation as affecting personal characteristics they tended to infer a role for the donor in the child's life, in contrast for those who see the donation as having a minimal impact.

Comparisons with tissue, organ and bone marrow donation were also common. Again, arguments typically focused on the genetic contribution, and whether or not the genetic contribution of mitochondrial DNA has significance over and above the avoidance of mitochondrial disease. A few noted that the mitochondrial donation is passed on via the germline, whereas any consequences of tissue donation are limited to the immediate recipient.

Many respondents raised the issue of the rights of the embryo and many of these suggested that mitochondrial donation for pronuclear transfer (PNT) differs from other donations, and is unacceptable because it involves the creation of an embryo with no intention of it being carried to term and born. Others argued that it is a misconception to regard the woman whose eggs are being used as the donor, seeing the mitochondria as being donated by egg or embryo, which they regard as a separate person. As this 'person' is unable to give informed consent to the procedure they concluded that it is unethical.

Respondents to the open consultation questionnaire were also asked, in a separate question, to choose between three models for rules to govern the disclosure of information to the child about the mitochondria donor. They also had the option of calling for another arrangement ('other'), or stating complete opposition to the introduction of the procedures. The largest number of respondents favoured this last option, while other choices divided fairly evenly between the models proposed as part of the question.

A substantial number of respondents expressed a preference for the model, outlining that no information or only information short of the identity of the donor should be disclosed. These respondents often saw maternal spindle transfer (MST) and PNT as more like blood or tissue donation than egg or sperm donation, and so concluded that the donor's identity need not be disclosed. Other arguments included that the child's proper understanding of the procedure is an important element in what information should be disclosed, or that the donation is best understood as an altruistic but impersonal act: *"...The child should have the right to know how they were conceived and why, but have it explained that their genetic characteristics such as physical traits, personality traits, intelligence etc. come from the parents they are growing up with."*

Respondents who favoured a model allowing the donor's information to be disclosed along with their identity once the child reaches 18 years of age, tended to feel more strongly about the consequences and significance of mitochondria replacement: *"If MST is legalised, such children should not be deprived of knowing their egg donor mother."* Their main concern was the medical, emotional or legal rights of children born through the procedure, which are sometimes explained as potential conditions determining what information should be disclosed. A number discussed the age requirement, normally agreeing that some limit is needed.

Several respondents felt it was important that donor consent should be sought to clarify which information is disclosed if a donor's identity would be made available to the child. Others argued that the disclosure of identity is part of the responsibilities of the donor.

A small number of respondents said they opposed the introduction of the techniques but think that if they were to be allowed, children should be able to know the identity of the donor.

Some respondents offered alternatives to the models proposed in the question, including suggestions for more flexible arrangements: *“It should be the choice of each donor as to what information is provided, along with any other conditions of their donation, and the choice of the parents as to whether to accept these conditions.”*

Summary

Views on this issue were mixed. Discussions at the deliberative public workshops indicated that those participants who supported the anonymity of the mitochondrial donor felt quite strongly that the rights of the donor should be protected and that donors should be given the choice as to whether they want their identity to be revealed to the child. On the other hand, there were also participants who felt that children should have the opportunity to know the identity of the donor, should they request it. At the end of the day, a larger number of participants favoured the anonymity of the donor. The ethics questionnaires revealed that almost half of participants (45% disagreed that any child born after these techniques should have the right to access the individual who donated the mitochondria, compared with 31% at the start of the day. However, the number of participants favouring a child's right to know about their donor did not vary greatly (33% at the start of the day to 31% at the end of the day), which indicates that these participants tended to remain steadfast in their views. Views were similarly varied at the Manchester open consultation meeting, although shifting of views throughout the course of the meeting cannot be assessed.

At the London open consultation meeting and in the patient focus group views appeared less varied. At the former people appeared to agree that mitochondria donors should be on a donor register as is the case with egg donors, but did not specify the level of detailed information to which a child should have access. However, it should be noted that we cannot say whether or not this was a majority view. In the focus group there was a strong view that donors should remain anonymous and that mitochondrial donation is more like blood donation than egg or sperm donation.

2.5 Regulation of mitochondria replacement

Deliberative public workshops

At the deliberative public workshops participants discussing safety and uncertainty about the risks of the new techniques felt that strong regulation would be needed. However, some expressed concern that although regulation and associated activities such as monitoring are important, the demands of the latter may be seen as too much of a burden for some parents and dissuade them from choosing one of the new techniques. Some people questioned how easy it is to track children born by these techniques over time if the parents are against being closely monitored.

A few participants in the deliberative public workshops picked up on concerns raised by a scientist in the video they were shown that even if the techniques are not licensed in the UK they are likely to become available in other countries with less stringent regulation regimes. Participants tended to agree that it would be important for these techniques to be introduced in a regulated environment. This point relates to discussions about the potential misuse of the technology, for example, to select for particular personal characteristics or create ‘designer babies’ rather than reduce the incidence of the disease.

Throughout discussions about the new techniques, participants felt that individual and personal choice for parents is paramount, this was supported by the results of the ethics

questionnaire. Participants were most likely to feel that couples themselves should make the decision about treatment (in consultation with their doctor), without the involvement of an expert regulator. This rose from 35% at the start of the day to 40% by the end of their discussions.

Public representative survey

Participants in the public representative survey were asked who should decide whether individual couples should have the treatment if the law is changed. Over a third of respondents (36%) favoured the option of couples being allowed to decide for themselves. A further 39% favoured some kind of involvement from a regulator – with one fifth (20%) favouring an expert regulator deciding on case-by-case basis (20%) and a similar proportion (19%) favouring an expert regulator approving clinics, with medical specialist deciding who to offer it to (19%). One quarter of respondents felt unable to express a preference.

Open consultation meetings

Participants at the open consultation meeting in London saw the need for regulation as highly important and argued that strict controls should be put in place to prevent illegal use of the techniques. Some felt that regulation is also necessary to counteract a potential slippery slope effect by warning that *“once you breach a principle such as allowing hybrids it creates a precedent.”* Some also suggested that those who are most at risk of passing the most severe forms of mitochondrial disease should be prioritised for treatment. In Manchester, participants suggested that the techniques should be regulated in a similar way to egg donation, with licenses being reserved for HFEA approved centres.

In the debate section of the Manchester consultation meeting, participants strongly felt that individual families should have the right to make the choice about whether or not to take advantage of the techniques: *“What we are saying is that there is the potential to have a different choice, and I think that if you don’t agree with it then you don’t have to have it, nobody would force you...If you do, and these techniques exist, well then I think it is unethical not to offer them. In my opinion, that is where there is a real ethical question.”*

Patient focus group

While this issue was not specifically discussed in the patient focus group, it was clear that most of the group place great importance on personal choice. One person said that if the techniques were licensed for clinical use, treatment should take place in a regulated environment.

Open consultation questionnaire

Respondents to the open consultation questionnaire were asked to indicate a preference for one of three possible models of regulation if the law were to be changed to allow mitochondria replacement to be carried out in specialist clinics. Almost half of the overall respondents declined to express such a preference, and instead selected a fourth option which allowed them to register an overall objection to mitochondria replacement being offered as a treatment under any circumstances. Respondents who chose this option tended to be of the opinion that no level of regulation could overcome the fundamental ethical objections to mitochondria replacement that they had already expressed in their answers to previous questions. A number of participants were also deeply sceptical about the

robustness of regulatory measures, often believing that their effectiveness would diminish over time.

Of those respondents who indicated a preference for a particular model of decision making, close to half (232 respondents) opt for a system in which clinics and individual patients would be free to make a case-by-case decision about whether or not to use mitochondria replacement, without any regulatory stipulations regarding which conditions or cases it may be suitable for. This preference was often associated with a view that a central regulatory board may lack sensitivity to individual circumstances and a feeling that individual patients should be empowered to choose the best option for their own families.

A similar number (242) of respondents preferred an option that includes a role for the regulator, the majority of which expressed a preference for a broad regulatory framework outlining those diseases that are deemed serious enough to warrant mitochondria replacement but which provided flexibility for patients and clinicians to reach individual decisions within this framework. A minority of respondents expressed a preference for the highest level of regulation: a model in which a central regulator would maintain responsibility for making decisions about particular cases.

Among those advocating a role for the regulator there was a wide feeling that an external regulatory framework would provide a buffer against abusive profiteering and a wide range of *'slippery slope effects'* which could otherwise ensue. It was also suggested that a central regulator would promote fairness by making sure that all applications for treatment would be judged according to the same criteria. Some proposed that the treatment should initially be reserved for those at risk of passing on the most severe forms of mitochondrial disease and ventured that: *"If and when no unexpected issues arise then perhaps it can be considered for other less severe mitochondrial diseases."*

Summary

In all the consultation strands participants argued that strong regulation is essential if the techniques are licensed for clinical use. Clinics themselves would need to be licensed and access to and use of the techniques should be regulated by a body such as the HFEA.

In discussions about who should make the decision about whether or not to use these techniques, there was a clear preference for individual choice; with parents and clinicians working together to agree what is the best option for them. This view did not appear to be affected by the level of knowledge or awareness people have about the disease or these techniques. The alternative to this would be for wider society to decide whether these treatments are allowed or not, it was felt to be unacceptable that a decision could be taken away from parents on the grounds that some of those within society are against the treatments being licensed.

2.6 Attitudes to legislation change

Deliberative public workshops

At the start of the second meeting of each of the deliberative public workshops participants were asked to record on a scale of 1 to 10 (1 = reject; 10 = support) their response to this question:

'If the treatment can be shown to be safe, to what extent would you support or reject it being made available to families through HFEA licensed clinics?'

Over the second day participants revisited this statement twice to help determine the extent to which new information, evidence and discussions have an impact on their support for the treatments. The overall mean score (across all three locations) at the start of the day was 8.2; however, after participants had discussed the ethical issues of using DNA from three people and germline therapy saw the mean figure rise to 8.4. This suggests that this group of participants remained steady in their support for the two techniques after deliberating these ethical issues. By the end of the day the mean score decreased to 7.8 and is likely to have resulted from concerns expressed by a small number of participants about the robustness of the scientific base. These concerns were raised by a scientist's reference in a video about a study on fish models that suggests a potential for mitochondrial DNA in cytoplasm to influence the formation of vertebrae¹⁰. This suggests that some participants' trust in the safety of these techniques was relatively fragile and easily disrupted by new information.

The deliberative public workshops concluded with participants developing '*messages for the Secretaries of State*' to consider when making their decisions about whether or not to license these techniques:

- Individual choice is important and parents should be able to use these techniques.
- Individuals need to be provided with all the relevant information they need to make an informed choice. This includes information on the potential and long-term risks, any uncertainties and the pros and cons of the two different techniques.
- The techniques must be introduced in a regulated environment.
- Parents who choose to access these techniques should be offered counselling.
- Donors should have confidentiality (although different views remain about whether some information should be available to the child).
- Fairness is an essential criteria and the techniques should be available to all, free of charge.
- The techniques are to be used to produce a healthy child for no other purposes.

Some other participants give more conditional support:

- A more comprehensive scientific assessment of the safety and efficacy must be completed; some participants expected to see human trials stage prior to wider licensing.
- There needs to be more information about how individuals will be able to access the techniques, with an emphasis on the importance of fair, equitable and affordable access.
- There needs to be more information about mitochondrial disease provided to the public, along with information on testing and diagnosis.

Public representative survey

This issue was not covered in the public representative survey.

¹⁰ The reference to this study was dropped from later versions of the video used in the consultation as it was not felt to be relevant because of the lack of transferability of the implications of it to humans and the fact it related to science rather than ethics

Open consultation meetings and patient focus group

Potential changes to the law were not discussed explicitly in the open consultation meetings, nor in the patient focus group; however, discussions at these events were broadly positive about the techniques overall. The 'key messages' section of the focus group report also demonstrates this positive sentiment. This could suggest that many of those in London, even more of those in Manchester, and participants in the focus group would probably support changing the law to allow these techniques to be made available in licensed HFEA clinics.

Open consultation questionnaire

In the open consultation questionnaire, respondents were asked whether they believe the law should be changed to allow mitochondria replacement techniques to be made available to people who are at risk of passing on mitochondrial disease to their child. The question was answered by 1,055 respondents. A majority of these respondents argued against changing the law, while a substantial minority argued in favour. A small number of respondents made a distinction between both techniques, almost exclusively saying they would support a law change for MST, but not for PNT. When answering this question many respondents referred to or reiterated arguments made in responses to earlier questions.

A small number of respondents made specific comments in relation to a possible change in the law. Those arguing against a law change sometimes referred to the international context and saw it as problematic that the UK would be the first or only country to allow the use of these MST and PNT. Several respondents argued that other methods should be considered before forging ahead with these new techniques: *"Other methods (such as repairing faulty mitochondria) are already being developed by scientists and should be examined further instead of considering PNT and MST."*

Respondents arguing in favour of law change, and particularly those adding caveats to their support, highlighted a variety of criteria they think need to be met. Most of these said that the techniques need to be proven safe and/or efficient before introducing legislation allowing them to be offered to people at risk of passing on mitochondrial disease. Respondents also suggested that further work needs to be undertaken to specify which of the techniques should be allowed, and in which circumstances: *"PNT raises more problems [for me], considering that it involves the destruction of potentially viable embryos. However, on the assumption that this would be performed at a very early stage, it might well be that the benefits are worth the worry if it becomes evident that PNT is safer and/or dramatically cheaper than MST."*

Summary

Participants in the deliberative public workshops discussed this issue specifically, with nearly 8 out of 10 supporting the techniques being made available. In the open consultation questionnaire those respondents who were against the techniques being made available tended to focus largely on ethical concerns, such as the use of embryos, and interference with the natural or spiritual aspect of reproduction. Based on the views and attitudes expressed in response to other issues, we think it is reasonable to conclude that most of those involved in other strands of the consultation apart from the open consultation questionnaire would support a change in the law that will allow these techniques to be used in a clinical setting.