Novel techniques for the prevention of mitochondrial DNA disorders:
an ethical review

NUFFIELD COUNCIL ON BIOETHICS

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The terms of reference of the Council are:

1. to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concerns;

2. to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other boy;

3. in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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* Dr MacKellar presented his views to the Working Group in a personal capacity, due to the limited timeframe of the Working Group's project and the longer frame required for the Council of the Scottish Council on Human Bioethics to submit an agreed opinion to the Working Group.

Foreword

Inherited mitochondrial disorders are progressive and often cause severely debilitating and disabling health problems. There is no cure for these conditions, and they can result in the death of babies, children and young people.

Mitochondria are tiny structures inside our cells which provide the energy for cells to function. Their failure to work properly can have devastating effects. Mitochondrial disorders can be caused by either problems in the genes in the nucleus affecting mitochondrial function, or by problems in genes within the mitochondria themselves. Recent years have seen increasing attention paid to two techniques both currently at the research stage: pronuclear transfer (PNT) and maternal spindle transfer (MST). These two IVF-based techniques seem to have the potential to prevent transmission of maternally-inherited mitochondrial disorders caused by mutations in the genes of mitochondria.

PNT involves using very early (one day old) embryos. MST uses unfertilised eggs. Both techniques would create embryos in which the nuclear genetic material of the intended parents is re-housed along with healthy mitochondria from a donated egg. This could come from either an unrelated donor or a maternal relative with healthy mitochondrial DNA. A maternal relative's healthy donated mitochondria would be identical to any healthy mitochondria the intended mother had, effectively permitting her to pass on what she may regard as 'her family's' mitochondrial DNA to her child.

There are important questions still to be clarified about the safety and efficacy of these two techniques. However, if they were successfully brought into clinical use they would allow women who would otherwise pass on mutated mitochondria through their eggs to their children to give birth to healthy children whilst using their own nuclear genetic material. Techniques such as these are currently unlawful for treatment use in the UK, because they would involve making changes to a human egg or embryo before transfer to a woman's body.

Patient groups and medical research funders are pressing the Government to offer Parliament the opportunity to vote to approve the use of regulation-making powers already in place which would allow such techniques for use in preventing the transmission of mitochondrial DNA disorders in the UK, at such time as they can be considered acceptably safe and effective. The granting of a licence by the Human Fertilisation and Embryology Authority (HFEA), the UK's fertility treatment and associated research regulator, to carry out research investigating PNT using human embryos to the Newcastle Fertility Centre at LIFE in 2005, and the promising results found there, have fuelled this pressure.

In January 2012, the Wellcome Trust announced funding of £4.4 million for a new Wellcome Centre for Mitochondrial Research located at the University of Newcastle, with additional university funding. The centre will undertake research intended to establish the safety and efficacy of PNT and MST as part of its work, while adding to knowledge about the techniques already gained from research in the UK and US. The Newcastle team estimate that, depending on the supply of donated eggs available to them, they will know in two or three years' time whether these techniques could become treatments.

On the same day as the Wellcome Trust's funding announcement, the Secretaries of State for Health, and for Business, Innovation and Skills tasked the Human Fertilisation and Embryology Authority and Sciencewise-ERC with seeking "public views on emerging IVF techniques designed to prevent the transmission of mitochondrial disease."[1] Together with previous requests for scientific information from the Secretary of State for Health to the HFEA, this makes it foreseeable that in the relatively near future Parliament could debate the approval of regulation-making powers in the Human Fertilisation and Embryology Act 1990 (as amended) to enable the techniques to be offered as treatments.

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[1] Human Fertilisation and Embryology Authority (19 January 2012) *HFEA to consult on ethics of 'mitochondria transfer'*, available at: http://www.hfea.gov.uk/6898.html".

Ethical considerations will be key to arriving at a robust and sustainable decision on whether the techniques should be offered as treatments. As an independent body, the Nuffield Council on Bioethics has sought to identify the novel ethical issues raised, while also looking deeper into the issues which have already featured in the public debate about these techniques.

Cell reconstruction techniques such as PNT and MST have attracted considerable interest partly because they would create children born with a genetic connection to three people. The new techniques also raise the question of whether seeking to rectify problems caused by mitochondrial genes is ethically different from seeking to rectify problems caused by genes in the nucleus, as mutations in either genome can be the cause of mitochondrial disorders.

Cell reconstruction techniques also raise familiar ethical questions common to many assisted reproduction treatments, such as determining the acceptable level of risk when using a new treatment in order to create a genetic connection between parents and children, and considering the issues that may arise where a donor helps to create a child.

We have explored these and other issues in preparing this report. The project lasted six months and included an open call for evidence and fact-finding meetings, which exposed us to a wide range of opinions and informed our thinking. We are grateful to the many people who gave us their views in the course of this. We hope that in turn, the questions we examine will assist policymakers, health professionals and the public in reaching their own conclusions on the key ethical issues raised by these new techniques.

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Terms of reference

(a) to identify and examine ethical issues relevant to the clinical use of techniques of *in vitro* mitochondrial transfer

(b) to elaborate these issues with a view to stimulating and informing further discussion, deliberation and debate

(c) to prepare a report on the above, to be delivered in Spring 2012

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Executive summary

The Nuffield Council on Bioethics conducted a six-month inquiry into the ethical issues raised by new techniques that aim to prevent the transmission of maternally-inherited mitochondrial DNA disorders. To assist with this enquiry, the Council appointed a Working Group with varied expertise, including in science, medicine, philosophy and ethics. The Working Group took evidence from and met people representing a wide range of opinion and prepared a report, adopted by the Council, which is intended to support and promote public debate around these important and difficult issues.

Introduction

Inherited genetic disorders caused by mutated mitochondrial DNA are progressive and can cause a wide spectrum of severe health problems including heart and other major organ failures, stroke, dementia, blindness, deafness and premature death. Symptoms of these disorders can appear at any time from birth, on a wide range of severity. There is currently no cure for these disorders.

New variations of IVF techniques are being developed that aim to replace damaged mitochondria by using part of a donated egg from a healthy individual. The intention is to allow women carrying disorders of mitochondrial DNA the chance to have healthy children that are genetically related to them, but born free of those disorders. Such techniques are not currently permitted for treatment use under UK legislation.

This report sets out the ethical considerations arising from the possible use of such techniques for treatment in the future. The issues that it discusses include:

- **Implications for identity**: the report considers a number of different notions of 'identity', discusses whether treatments for mitochondrial disorders might affect identity in some ways, and considers what significance this might have with regards to the acceptability of such treatments.

- **Germline therapies**: the Working Group concluded that donation treatments for mitochondrial disorders would constitute a form of germline gene therapy. The report discusses various concerns about germline therapies, and how treatments involving mitochondrial DNA might differ from other types of germline therapy.

- **The introduction of novel techniques and follow-up of children**: all treatments – new and established – are likely to involve some degree of risk and need to be regarded as experimental when first introduced. However, given the germline effects of mitochondrial donation techniques, particular issues are discussed concerning the ways in which any future treatment would need to be regulated and monitored, with follow-up of the families concerned.

- **Parentage of the child:** mitochondrial donation techniques involve the introduction of mitochondrial DNA from a donor, so the resulting child would be born with a genetic contribution from a third party. The report discusses the potential significance of this in biological, social and legal contexts.

- **The status of the mitochondrial donor**: the mitochondrial donor would go through the same procedures as a reproductive egg donor does when donating eggs for fertility treatments. The report considers whether the two types of donation should be treated in similar ways, or whether there are significant differences in terms of how the mitochondrial donor should be regarded, and the regulatory implications of this.

- **Implications for wider society and future generations**: some people suggest that as mitochondrial DNA is inherited from the egg, any future mitochondrial donation treatments should be limited to creating boys so that possible adverse future impacts will not be passed on. This issue is discussed, as well as questions about attitudes towards people with mitochondrial disorders, and about other possible future uses of the techniques.

After considering all of these questions, and others, and having heard from a wide range of contributors, the Working Group identified a number of issues that require further consideration. The Council believes that continuing debate about these issues will be important, but it also reached a number of conclusions that the Government and others may wish to consider.

Conclusions and issues for further consideration:

- Due to the health and social benefits to individuals and families of living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children, on balance we believe that if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them, if they wish to do so and have been offered an appropriate level of information and support.

- Given the above and subject to the appropriate oversight, we believe that as a research objective it is ethical to gather further information about pronuclear transfer and maternal spindle transfer in order that they can be considered for treatment use.

Treatment as part of a research trial

We believe that in the first instance, novel techniques such as pronuclear transfer and maternal spindle transfer (or any comparable future treatment) should only be offered as part of a research trial in centres specialising in mitochondrial disorders. Consent to follow up would need to be included as a mandatory part of parental consent to participation in the trial.

Regulation: follow-up

Families using such techniques should commit to allowing very long term follow-up of their children and families in order to further knowledge about the outcomes of these techniques. To support this aim we would recommend the creation of a centrally funded register of any such procedures performed in the UK, accessible to researchers over several decades.

Parentage of the child

Although the perception of the personal and social relationships created by egg or embryo reconstruction would be essentially a matter for the individuals concerned, it is the view of the Working Group that mitochondrial donation does not indicate, either biologically or legally, any notion of the child having either a ‘third parent’, or ‘second mother’.

Regulation: status of the mitochondrial donor

The donor of mitochondria should not have the same status in regulation as a reproductive egg or embryo donor in all aspects. As part of this, we do not believe mitochondrial donors should be mandatorily required to be identifiable to the adults born from their donation.

Further issues for discussion

The novel treatments under discussion were viewed by the Working Group as examples of germline therapies. The wider policy debate could benefit from a fuller discussion of the ethics of the different kinds of prospective and theoretical germline therapies than was possible within the remit of this report. This would include potential therapies that would act on the cell nucleus with heritable effects, and therapies which might involve nuclear transfer in its various forms.

Chapter 1

Mitochondrial disorders and current treatment options

Chapter 1 - Mitochondrial disorders and current treatment options

Introduction

1.1 Mitochondria are organelles; small structures present in all cells of the human body in multiple copies which can only be seen with an electron microscope.[2] Enzymes in mitochondria convert the nutrients received from food into cellular energy. This is essential to the functioning of cells in the human body. Mitochondria have been described as 'the powerhouse of the cell', and have sometimes been referred to as the 'batteries in a cell', due to their generation of energy.

1.2 Energy is needed for cells to proliferate, to move or contract, and to generate and process signals so that tissues and organs can function properly.[3] Serious health problems can arise if mitochondria are not able to function at levels sufficient to meet the energy demands of our cells or tissues. Mitochondria also contribute towards the maturation of sperm and eggs, embryonic development and programmed cell death.[4]

1.3 Mitochondria are found in the cell cytoplasm, which is a usually jelly-like fluid inside the cell that surrounds the nucleus and fills the cell. Mitochondria are thought to have originated as primitive bacteria which, billions of years ago, took up residence in the cytoplasm of cells of other organisms. Over thousands of generations, some of the genetic information from these bacteria has migrated into what have become human cell nuclei, while the mitochondria now exist separately within our cell cytoplasm, retaining their own independently-replicating DNA. In 1963, it was discovered that mitochondria contain their own DNA system (mtDNA).[5] In 1981, the mitochondrial genome became the first complete sequence of a human genome to be published.[6] The human mtDNA sequence was reanalysed and revised in 1999, correcting sequence errors in the initial publication.[7] Mitochondrial genes operate differently from nuclear genes and their activities and relationship to the nuclear genome are complex and not always well understood.

1.4 A cell in an adult's body may contain from a few hundred to several thousand mitochondria. The number of mitochondria in cells depends on the type of cells or the type of tissue that those cells constitute. This can reflect the differing amounts of cellular energy that each tissue type needs in order to function properly.[8]

1.5 Normal mitochondrial functioning and replication involve both genes in the cell nucleus and genes in the mitochondria working together. The 20-30,000 genes (approximately) – around 99.9 per cent of our genes in total – typically contained in the nucleus of a cell provide the basis for how human bodies are built and for many of our unique personal characteristics.[9]

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2 One mitochondrion can be around 0.5 by 1µm (micrometres) long although the size varies greatly. They are typically many times smaller than other body cells. See: Rice University (2005) *Structure of mitochondria*, available at http://www.ruf.rice.edu/~bioslabs/studies/mitochondria/mitotheory.html.

3 St John J, and Lovell-Badge R (2007) Human–animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate *Nature cell biology* **9**: 988-92, Box 1.

4 Spikings EC, Alderson J, and John JCS (2006) Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer *Human Reproduction Update* **12**: 401-15.

5 Nass S, and Nass MMK (1963) Intramitochondrial fibers with DNA characteristics *The Journal of cell biology* **19**: 613-29.

6 Anderson S, Bankier A, Barrell BG *et al.* (1981) Sequence and organization of the human mitochondrial genome *Nature* **290**: 457-65.

7 Andrews RM, Kubacka I, Chinnery PF et al. (1999) Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA Nature Genetics **23**: 147.

8 St John J, and Lovell-Badge R (2007) Human–animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate *Nature cell biology* **9**: 988-92.

9 Taylor RW, and Turnbull DM (2005) Mitochondrial DNA mutations in human disease *Nature Reviews Genetics* **6**: 389-402.

1.6 By contrast, the 37 genes contained in the mitochondria (around 0.1 per cent of our genes in total) are thought to be restricted to governing the actions of the mitochondria. Thirteen of the genes in mitochondria are protein-encoding genes associated with the generation of cellular energy. The remaining 24 genes (22 tRNAs and 2 rRNAs) in the mitochondria assist the 13 protein genes to produce proteins.[10] It is possible that mitochondrial DNA may have other influences, but this is the subject of ongoing scientific enquiry and debate. For example, some authors studying the mitochondria of mice have suggested a link between the functioning of their mitochondria and their cognitive capabilities.[11]

1.7 It is important to note that, in many cases, the biological function of some nuclear genes and of mitochondrial DNA genes is identical. For example, the mitochondrial enzyme Complex I, which is crucial to cellular energy production, contains seven mitochondrial DNA encoded subunits and 35 encoded by nuclear genes. In general, most nuclear genes encode proteins with a biological function, just as mitochondrial genes do, so in some aspects there are very few important distinctions that can be drawn between the two locations in which genes are found.

1.8 Mitochondrial genes pass down the generations via a different mechanism from the genes in the nucleus, which we receive from our mother and father. Women pass on mitochondrial DNA to their children via the mitochondria in their eggs. The hundreds of thousands of mitochondria in the fertilised egg divide among the 'daughter cells' during embryonic development and replicate to populate every cell in the resulting person.

1.9 Although mitochondria are maternally inherited, our mitochondrial DNA links us to successive generations of our maternal family rather than to any one individual. The mitochondrial DNA of close relatives such as our mother, brothers and sisters, maternal grandmother, maternal aunts and uncles are likely to be nearly identical, so it would not be possible to identify our mother's mitochondrial DNA from within this group. This aspect of mitochondrial DNA inheritance has been useful to scientists in missing person's cases, for example, allowing a genetic match to be made after an individual has been separated from his or her maternal relatives, even if their parents have since died and there are few surviving relatives.

1.10 Men carry mitochondrial DNA and will be affected by mitochondrial disorders where there is a sufficiently high proportion of mutated mtDNA. However, they are not thought to pass their mitochondria on to their children. Sperm contain mitochondria, which are used to help power their movement but immediately after fertilisation these paternal mitochondria degenerate as the male pronucleus forms in the fertilised egg. Only one study has found paternal mitochondria to persist naturally after fertilisation (in muscle tissue only),[12] and there is no published evidence of father-to-child transmission of an inherited mitochondrial disorder.[13]

[10] Anderson S, Bankier A, Barrell BG *et al.* (1981) Sequence and organization of the human mitochondrial genome *Nature* **290**: 457-65.

[11] Roubertoux PL, Sluyter F, Carlier M *et al.* (2003) Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice *Nature Genetics* **35**: 65-9; Moreno-Loshuertos R, Acín-Pérez R, Fernández-Silva P *et al.* (2006) Differences in reactive oxygen species production explain the phenotypes associated with common mouse mitochondrial DNA variants *Nature Genetics* **38**: 1261-8.

[12] Schwartz M, and Vissing J (2002) Paternal inheritance of mitochondrial DNA *New England Journal of Medicine* **347**: 576-80.

[13] Brown DT, Herbert M, Lamb VK *et al.* (2006) Transmission of mitochondrial DNA disorders: possibilities for the future *The Lancet* **368**: 87-9.

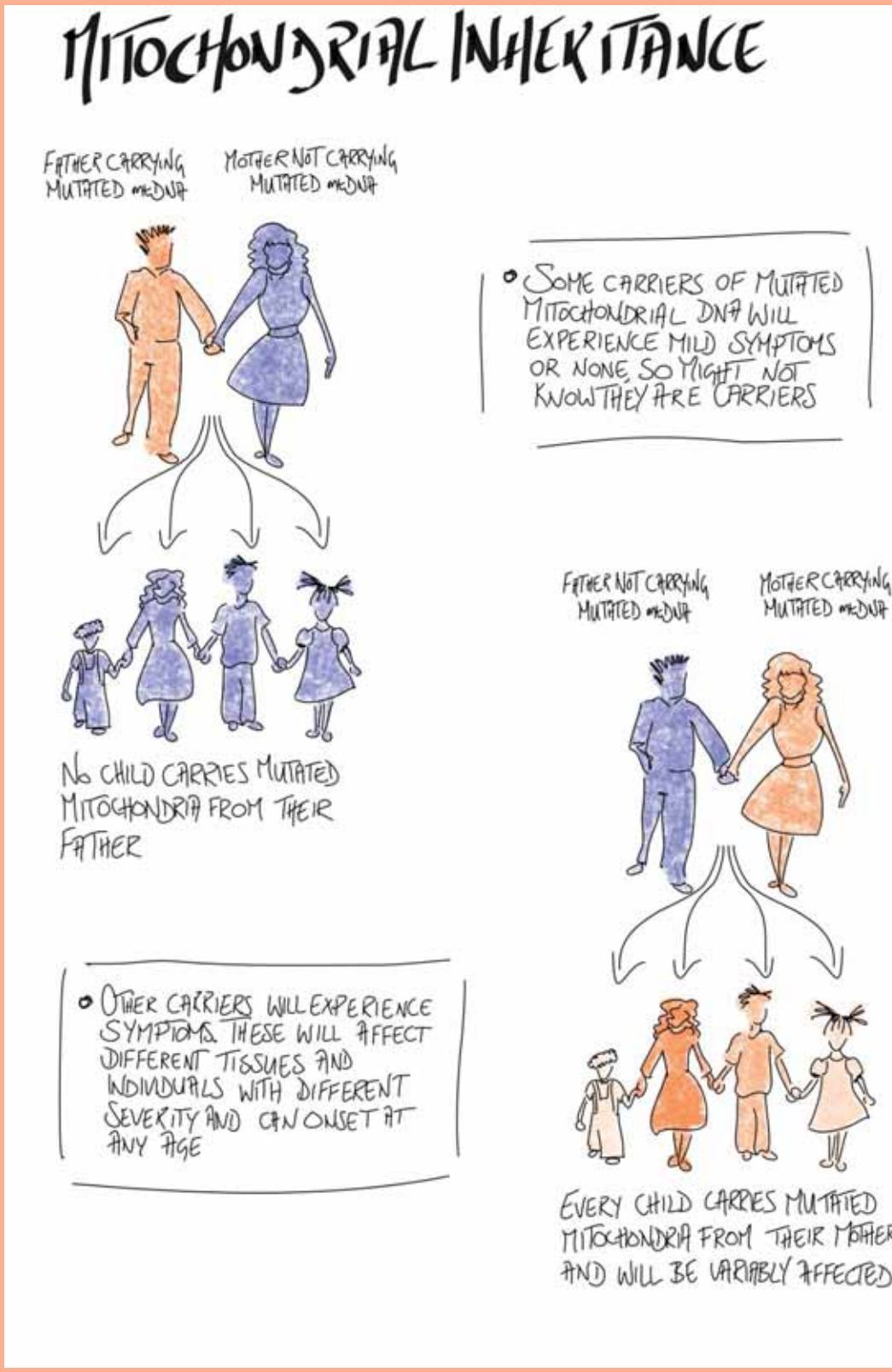

Illustration by Rebecca Kent

Mitochondrial disorders

1.11 Mitochondrial disorders can arise from two sources: mutations of DNA in mitochondria, or mutations of DNA in nuclear genes. Mitochondrial DNA has a mutation rate of about ten times that of nuclear DNA.[14] This may be because there are so many more mitochondria per cell compared with two pairs of nDNA genes per cell, and also that the system of replication of mitochondria is prone to errors due to less efficient systems for DNA repair.[15]

1.12 At present there is no cure for people with mitochondrial diseases resulting from either source, and many of their symptoms cannot be treated. A helpful summary of some of the disorders caused by mutated mitochondrial DNA is provided in a report provided to the Secretary of State for Health, convened by the HFEA in 2011.[16] Our report primarily discusses techniques that researchers are developing with the aim of preventing the transmission of mutated mitochondrial DNA which can cause mitochondrial disorders. These techniques would not be able to prevent the transmission of mitochondrial disorders caused by nuclear DNA.

1.13 Mitochondrial disorders have been described as "…a cruel class of inherited disease, because serious, even life threatening conditions are coupled with great unpredictability about how future children will be affected."[17] They are progressive, can be very seriously debilitating and disabling. They may also cause miscarriage and stillbirth, death in babies, children and young people, or severe symptoms which onset in adulthood. The symptoms and the age and severity at which they are experienced vary widely between patients, which can make diagnosis difficult. Mitochondrial disorders may affect one organ at a time – for example resulting in blindness or heart failure – or may affect several areas of the body at the same time. Mothers can pass on mitochondrial disorders without having experienced symptoms themselves, which in some cases may mean that they are not aware that they carry mutated mitochondrial DNA that can cause disorders in their children.

1.14 Loss of normal cellular energy production caused by mitochondrial mutation often has the most impact on organs of the body with a relatively high need for energy. This is why severe symptoms may be experienced in the brain, heart, kidneys and major muscle groups. Symptoms of mitochondrial disorders caused by mitochondrial DNA and nuclear DNA can include: poor growth, loss of muscle coordination, muscle weakness, exercise intolerance, diseases and malfunctions of the neuromuscular system, confusion, disorientation and memory loss, neurological problems, seizures, autism or being on the autistic spectrum, developmental delays, learning disabilities, hearing and/or vision loss, heart, liver, kidney or respiratory disease (which may progress to heart and/or liver failure), gastrointestinal disorders, diabetes, thyroid and/or adrenal dysfunction, lactic acidosis, and immune system problems resulting in an increased susceptibility to infections.[18]

[14] Yakes FM, and Van Houten B (1997) Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress *Proceedings of the National Academy of Sciences* **94**: 514-9.

[15] Linnane AW, Marzuki S, Ozawa T, and Tanaka M (1989) Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases *Lancet* **1**: 642.

[16] Human Fertilisation and Embryology Authority (2012) *Review of scientific methods to avoid mitochondrial disease 2011*, available at: http://www.hfea.gov.uk/6372.html, annex A: clinical disorders due to mutations in mtDNA, at p25.

[17] North East England Stem Cell Institute (2008) *Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation*, available at: http://www.nesci.ac.uk/assets/docs/NESCIbriefon2008HFEbill-MitochondrialTransplants-Vers01-6.pdf, p2.

[18] Mito Action (2008) *A clinician's guide to the management of mitochondrial disease*, available at: http://www.mitoaction.org/guide/table-contents.

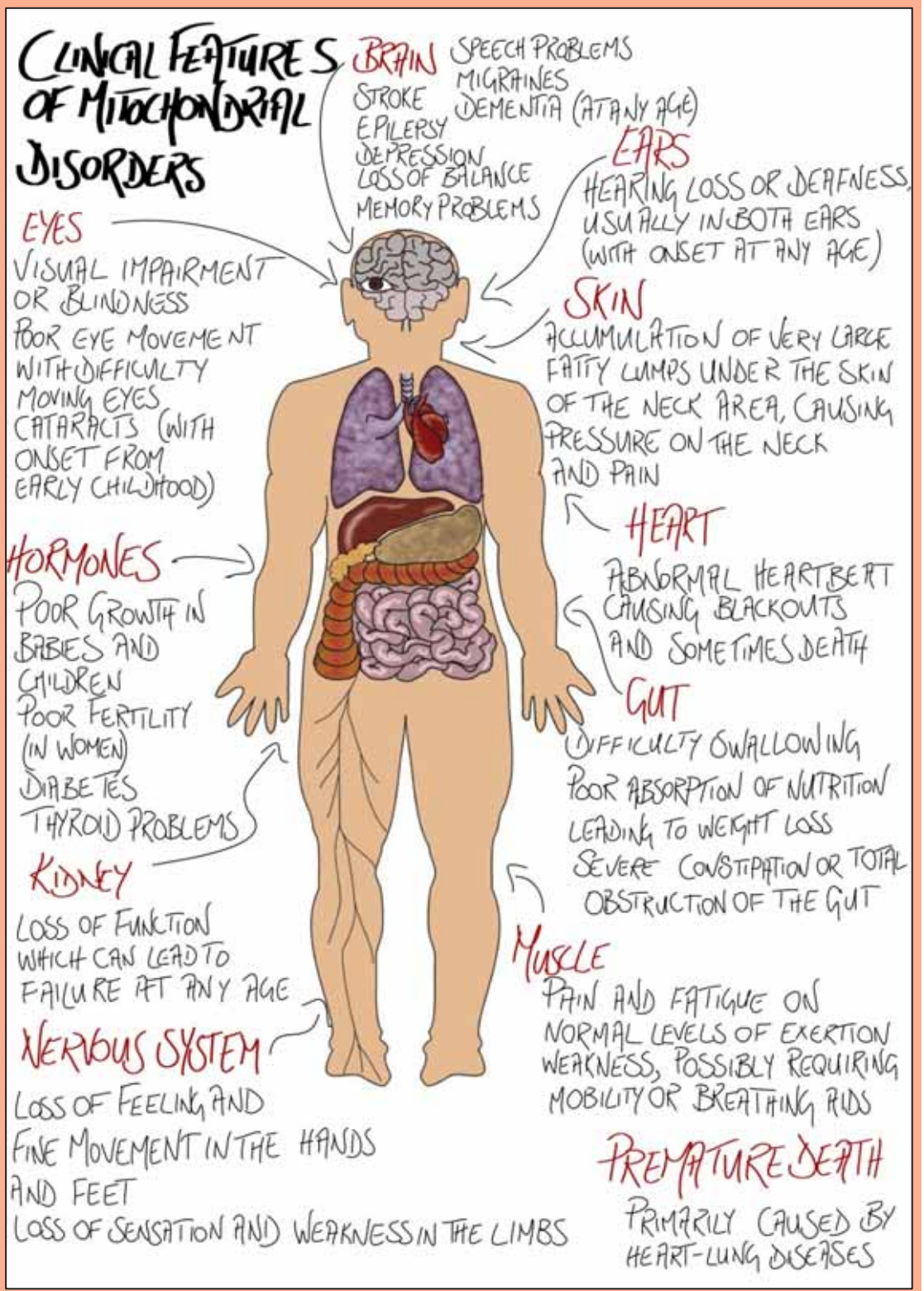

Illustration by Rebecca Kent

1.15 When a cell contains only one type of mitochondrial DNA (mtDNA), this is known as homoplasmy. The majority of people have a near-homoplasmic population of normally-functioning mitochondria. Mechanisms exist in natural human fertilisation which may contribute towards maintaining homoplasmy as we reproduce.[19] However, these mechanisms are not always able to ensure this and most people carry some abnormal mitochondria, but these do not generally cause health problems. It is rare, but possible, for people to have a homoplasmic population of mutated, abnormally-functioning mitochondria, which are likely to cause serious health problems, including early death. In unusual cases, homoplasmy may not produce symptoms for the carrier, but can cause devastating problems for her children.[20]

1.16 When a cell contains two or more types of mtDNA, this is known as heteroplasmy. This term is used for cells with a mixed population of mutated and normal mtDNA. Heteroplasmy is also used to describe a cell containing a combination of normally-functioning mtDNA variants, for example when they have been brought together from different women's eggs via cell reconstructive technologies.

1.17 Patients with the symptoms of mitochondrial DNA disorders are therefore likely to have mutations either in a high proportion of their mitochondria (heteroplasmy) in the affected tissues or, when viable, in all of the mitochondria (homoplasmy). The percentage of mutated mitochondria may vary among tissues and may change over time. Generally, as the proportion of mutated mitochondria becomes higher, progressively more severe symptoms will result. Depending on the type of tissue that a cell constitutes and the type of mtDNA mutation, when the mutated mitochondria make up around 60 per cent or more of the total in a cell,[21] (known as a high 'mutant load') this can cause health problems. However, the relationship between the percentage of mutated mitochondria and clinical symptoms is not straightforward, as the threshold at which problems are caused varies between tissues and among different types of mitochondrial mutation. Individuals may also tolerate a high mutant load differently. Even siblings may experience a different severity of symptoms, despite a similar level of mitochondrial mutation. This could be due to environmental factors, behaviour – such as physical exercise – or the action of each individual's nuclear genes.

1.18 However, when female carriers of mtDNA mutations have children, even a small proportion of mutated mitochondria in the founding cells can cause serious health problems. In reproduction, a small number of the woman's mitochondria are selected to populate all the cells of the resulting child in much greater numbers, a phenomenon known as the 'mitochondrial bottleneck'. This means that even women with a low or undetectable proportion of mutated mitochondria in their somatic cells can produce some eggs with a higher than expected mutant load, or even homoplasmy of mutated mitochondria. The chance of having eggs with a high mutant load is increased in those carriers who have a high mutant load in their other body tissues. This mechanism explains the extreme and hard-to-predict shifts in the proportion of healthy-to-mutated mitochondria, from zero per cent to 100 per cent that can occur between mother and child, and between siblings.

1.19 It is thought that variants of mtDNA might have replicative advantages over each other, which could partly explain why copies of mitochondria that eventually populate a child's somatic cells may not mirror the proportion of healthy-to-mutated mitochondria within the egg cell that created him or her.[22]

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[19] Spikings EC, Alderson J, and John JCS (2006) Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer *Human Reproduction Update* **12**: 401-15.

[20] McFarland R, Clark K, Morris A *et al.* (2002) Multiple neonatal deaths due to a homoplasmic mitochondrial DNA mutation *Nature Genetics* **30**: 145.

[21] Taylor RW and Turnbull DM (2005) Mitochondrial DNA mutations in human disease *Nature Reviews Genetics* **6**: 389-402.

[22] Blok RB, Gook DA, Thorburn DR and Dahl HHM (1997) Skewed segregation of the mtDNA nt 8993 (TRG) mutation in human oocytes *The American Journal of Human Genetics* **60**: 1495-501.

1.20 In an embryo, homoplasmy of mutated mitochondria or heteroplasmy with high levels of mutated mitochondria may mean that it does not implant and establish as a pregnancy, or is miscarried at an early stage. However, for many mutations this is not the case; these mitochondrial mutations do not threaten fetal viability or the adequate functioning of fetal cells until *after* birth, when the child independently converts food energy into cellular energy. The replication of mtDNA which occurs mainly during fetal development might explain why the onset of symptoms of some mitochondrial disorders occurs in babies and young children.[23]

1.21 The mechanisms that regulate the number of mitochondria within different cell types are not well understood.[24] The numbers of mitochondria in the germline fluctuate dramatically throughout the developmental stages of the egg to the point of fertilisation, and also after fertilisation to the implanted embryo, and then to fetal and child development.[25] The scale of these changes can be observed in mice, where an unfertilised egg cell contains more than 100,000 mitochondria, reflecting the energy demands of fertilisation and early development, before mtDNA replication starts.[26] Each cell of an embryo at blastocyst stage then contains around 1,000 mitochondria, and after the embryo implants, primordial germ cells contained in the early embryo may contain as few as ten mitochondria.

Current treatment options

1.22 Whether caused by mutations in mitochondrial genes or in nuclear genes related to mitochondrial function, mitochondrial disorders are relatively rare in the population. A study in 2008 found that one in 200 children is born each year with a disease-causing mitochondrial DNA mutation, but in most cases these are due to a very low mutation load these cause only mild forms of mitochondrial disorders or are asymptomatic. However, these pathogenic mutations could nonetheless be passed on to future children at more significant levels.[27] It was also previously thought that least one in 8,500 of the population carried mitochondrial DNA mutation with a disease-causing mutation load.[28] It has been calculated that at least 3,500 women in the UK, many of whom are of childbearing age, carry a potentially problematic level of mtDNA mutation, but this may be an underestimate.[29]

1.23 It is difficult to be precise as to how many people are affected by mitochondrial DNA disorders, as there is thought to be a high rate of under-diagnosis and misdiagnosis due to the wide range and varying severity of the symptoms experienced. It can also be hard to establish whether a mitochondrial disorder has been caused by problems in nuclear genes or mitochondrial genes. New mitochondrial disorders are also still being identified. An estimated figure for the total prevalence of people affected by mitochondrial DNA disorders and mitochondrial disorders caused by nuclear genes is 1 in 5,000,[30] and in a response to the Working Group's call for evidence, the Medical Research Council and the Wellcome Trust also commented on prevalence: "Abnormal mtDNA is present in about one in 250 live births. Although many of these cases will not result in significant symptoms, at least one in 10,000 adults in the UK are severely affected by mitochondrial disease. Researchers at Newcastle University currently care for over

[23] Sato A, Kono T, Nakada K *et al.* (2005) Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation *Proceedings of the National Academy of Sciences of the United States of America* **102**: 16765-70; Wallace DC (1999) Mitochondrial diseases in man and mouse *Science* **283**: 1482-8.

[24] St John J, and Lovell-Badge R (2007) Human–animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate *Nature cell biology* **9**: 988-92, box 1: the biology of the mitochondrion.

[25] The Rare Mitochondrial Disease Service for Adults and Children (2009) *New approach to prevent inheritance of* mitochondrial *disease*, available at: http://www.mitochondrialncg.nhs.uk/research.html.

[26] St John J, and Lovell-Badge R (2007) Human–animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate *Nature* cell *biology* **9**: 988-92.

[27] Elliott HR, Samuels DC, Eden JA, Relton CL, and Chinnery PF (2008) Pathogenic mitochondrial DNA mutations are common in the general population *The American Journal of Human Genetics* **83**: 254-60.

[28] Schaefer AM, Taylor RW, Turnbull DM, and Chinnery PF (2004) The epidemiology of mitochondrial disorders—past, present and future *Biochimica et Biophysica Acta (BBA) - Bioenergetics* **1659**: 115-20.

[29] Brown DT, Herbert M, Lamb VK *et al.* (2006) Transmission of mitochondrial DNA disorders: possibilities for the future *The Lancet* **368**: 87-9.

[30] Schaefer AM, Taylor RW, Turnbull DM, and Chinnery PF (2004) The epidemiology of mitochondrial disorders—past, present and future *Biochimica et Biophysica Acta (BBA) - Bioenergetics* **1659**: 115-20.

400 patients with mitochondrial disease. Research on this cohort of patients has highlighted the following issues: a) 50-60 per cent of all children with mitochondrial disease do not have a genetic diagnosis and 40 per cent of these children have a generalised defect of mtDNA expression. Being able to establish the genetic basis in these patients will enable specific genetic advice and the ability to suggest new approaches to treatment."[31]

1.24 However, bearing in mind the limiting factors listed above, a widely-quoted figure (approximated from different published papers) is that around one in 6,500 children is thought to develop a more serious mitochondrial disorder, where some of these disorders can be fatal.[32] In the context of neuromuscular disease, this figure would make mtDNA disorders one of the most common inherited neuromuscular disorders.[33]

1.25 To put these figures into context, sickle cell anaemia is one of the most common genetic disorders. It is estimated that there are around 12,500 people with sickle cell anaemia in England, and one baby in every 2,000 is born with the condition.[34] Cystic fibrosis (CF) is one of the UK's most common life-threatening genetic disorders. Over two million people in the UK carry a mutation that causes CF, around 1 in 25 of the population. CF affects between one in 2,000 and one in 2,500 children.[35]

1.26 In respect of mitochondrial disorders caused by mutations in mitochondrial DNA, given the very poor outcomes for some of the children and young people affected, techniques have been sought that could prevent the transmission of mutated mtDNA. Researchers expect that if proven to be safe and effective in future, the two experimental techniques which we primarily examine in this report, pronuclear transfer (PNT)[36] and maternal spindle transfer (MST),[37] would result in children born free from inherited mitochondrial disorders caused by mutated mtDNA.

1.27 PNT and MST could be offered with IVF to women who wish to use their own eggs to have a baby but who risk passing on a disease-causing level of mutated mitochondria to their children. No licensed technique is currently available which could meet both of these criteria, so there has been great interest in these techniques. PNT and MST would only be able to prevent those disorders caused by mutated mitochondria.

1.28 Where mutations in *nuclear* DNA create a risk of inherited mitochondrial disorders, some parents may have existing options to minimise, or avoid, this transmission to their children. If the responsible mutation(s) have been identified in other members of the family, nuclear-encoded mitochondrial problems in an established pregnancy can be identified by prenatal diagnosis (PND), which samples cells in pregnancy in order to gather genetic information. Alternatively, parents can be offered IVF with preimplantation genetic diagnosis (PGD) conducted on their *in vitro* embryos, which may or may not be followed by confirmatory PND if a pregnancy is established. PGD is a process used with IVF techniques, in which one or more cells are

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[31] The Medical Research Council and the Wellcome Trust, responding to the Working Group's call for evidence, paragraphs 6-6a.

[32] Schaefer AM, McFarland R, Blakely EL *et al.* (2008) Prevalence of mitochondrial DNA disease in adults *Annals of Neurology* **63**: 35-9.

[33] Darin N, Oldfors A, Moslemi AR, Holme E, and Tulinius M (2001) The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities *Annals of Neurology* **49**: 377-83; Skladal D, Halliday J, and Thorburn DR (2003) Minimum birth prevalence of mitochondrial respiratory chain disorders in children *Brain* **126**: 1905-12; Department of Health (19 January 2012) *Views sought on changing the law to find cure for inherited mitochondrial disease*, available at: http://www.dh.gov.uk/health/2012/01/mitochondrial/.

[34] NHS Choices (2010) *Sickle cell* anaemia, available at: http://www.nhs.uk/conditions/Sickle-cell-anaemia/Pages/Introduction.aspx.

[35] Boat T, Welsh M, and Beaufet A (1995) Cystic fibrosis, in *The metabolic basis of inherited disease*, Scriver C, Beaudat A, Sly W, and Valle D (Editors) (New York: McGraw-Hill), pp 2649-80.

[36] Craven L, Tuppen HA, Greggains GD *et al.* (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease *Nature* **465**: 82-5.

[37] Tachibana M, Sparman M, Sritanaudomchai H et al. (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells Nature 461: 367-72.

removed from an *in vitro* embryo for genetic testing. Some families may wish to use this information in order to make a decision about establishing or continuing with a particular pregnancy. However, identification of the nuclear genes responsible for mitochondrial disorders is still at an early stage, so this option cannot be offered to all patients at risk of having a child with a mitochondrial disorder caused by mutations in nuclear DNA.

Current options for preventing the transmission of inherited mitochondrial DNA disorders

1.29 The risks of transmitting mitochondrial DNA disorders are complex and difficult to predict, and will differ depending on the proportion of mutated mitochondria carried by the affected woman''s egg. In general, women with homoplasmic mutations pass on a homoplasmic mutant load to their children, whereas the load passed on by women with heteroplasmic mutations is variable and unpredictable. How severely a child may be affected, if at all, may be very hard to determine before birth, as this will also depend on the particular mutation, and in what way the mutation affects the functioning of the body and at what age these symptoms manifest.

1.30 Women who have experience of living with mitochondrial disorders themselves, or who have affected family members, may not want to risk having a child who could be similarly affected. For this group, the only way of avoiding having an affected child would be to choose not to use their own eggs to conceive. Therefore, women in this position may, for example, decide to seek egg donation, surrogacy with egg donation, or to apply for adoption.

Current options for minimising the risk of transmission of inherited mitochondrial DNA disorders

1.31 The Working Group's remit did not extend to the consideration of ethical issues pertinent to preimplantation genetic diagnosis (PGD) *per se*, which might include justifications for undertaking genetic testing on embryos, embryo selection and destruction, and related issues of choice, consent and autonomy. Nor did its remit extend to the consideration of ethical issues pertinent to prenatal testing *per se*, including instances where decisions are made about a pregnancy when test results are not entirely clear. This may be particularly relevant to some instances of mitochondrial DNA disorders. In addition, the Working Group's remit did not encompass the consideration of ethical issues pertinent to termination for fetal abnormality and questions of choice, consent and autonomy engaged in this.

1.32 At present, heteroplasmic women who would like to use their own eggs to have a baby may have a number of options available to them in order to minimise their risk of passing on mitochondrial DNA disorders to their child.[38] This group of women may, for example, be offered PGD as part of an IVF cycle prior to pregnancy, and/or prenatal diagnosis (PND) once a pregnancy is established. Neither technique would be offered to homoplasmic women due to the inevitability that the embryo or fetus would also be homoplasmic for the mutation.

Preimplantation genetic diagnosis (PGD)

1.33 PGD is a process used with IVF techniques, in which one or more cells are removed from an *in vitro* embryo for genetic testing. PGD has "extended the scope of IVF beyond the treatment of infertility", which in turn has made new treatments possible.[39] In 2009, the most recent year for which UK figures are available, 232 patients underwent 288 PGD treatment cycles in the UK,

[38] Poulton J, Kennedy S, Oakeshott P, and Wells D (2009) Preventing transmission of maternally inherited mitochondrial DNA diseases *BMJ* **338**.
[39] BioNews (13 February 2012) Beyond the treatment of infertility, available at: http://www.bionews.org.uk/page_124715.asp.

resulting in 86 live births and 100 babies. The live birth rate (births per PGD cycles started) was 29.9 per cent in 2009.[40]

1.34 For heteroplasmic women, but not for cases of homoplasmic mutation, PGD sampling of two cells can be used to identify which, if any, of their embryos contain a sufficiently low level of mutated mitochondria. Based on this information, women or couples may decide to go ahead with, or to avoid, transferring specific embryos to the woman's womb with the aim of beginning a pregnancy. The opportunity to make decisions based on information gathered at the pre-implantation stage may be viewed by patients as preferable to making decisions about an established pregnancy. This patient group may also already have experience of repeated termination of pregnancy or miscarriage because of mitochondrial problems.

1.35 The first report of a healthy baby born following PGD was in 2006, where the child's family was affected by the mitochondrial DNA mutation NARP.[41] NARP, which stands for Neurogenic Muscle weakness, Ataxia, Retinitis Pigmentosa, primarily affects the nervous system with onset in childhood or young adulthood. Symptoms can include limb numbness or pain, muscle weakness, balance and physical coordination problems, visual loss which may progress to blindness, learning disabilities, developmental delays or dementia, seizures, hearing loss and heart problems.[42]

1.36 The HFEA in the UK has since licensed PGD for NARP and other mitochondrial disorders including MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes),[43] Leigh's Syndrome (subacute necrotising encephalopathy of childhood)[44] and MERRF (Myoclonic Epilepsy and Ragged Red Fibers)[45]. In 2009, a UK team was granted a licence to perform PGD for these four named conditions.[46] The HFE Act permits embryo testing where one or more of the following purposes apply: "a) establishing whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth', or '(b) in a case where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality".[47] For each named mtDNA *condition* – rather than mutation – an HFEA licence committee decides whether it can be licensed for PGD.

1.37 However, because many of the different types of mtDNA mutation are inherited in a complex and sometimes poorly-understood way, for many families PGD has not been useful because information gathered from their embryos has not permitted doctors to offer a clear prognosis for any prospective child. This can be due to the fact that individuals tolerate similar mutant loads differently, and also that the level at which the mutant load in cells causes problematic symptoms varies for different types of tissue in the body, making it difficult to determine a

[40] HFEA (2012) Latest UK pre-implantation genetic diagnosis (PGD) figures – 2009, available at: http://www.hfea.gov.uk/1271.html.

[41] Steffann J, Frydman N, Gigarel N *et al.* (2006) Analysis of mtDNA variant segregation during early human embryonic development: a tool for successful NARP preimplantation diagnosis *Journal of Medical Genetics* **43**: 244-7.

[42] For more information and case reports about NARP, see: Online Mendelian Inheritance in Man (2011) *516060: ATP synthase 6; MTATP6*, available at: http://omim.org/entry/516060.

[43] Online Mendelian Inheritance in Man (2011) *590050: transfer RNA, mitochondrial, leucine 1; MTTL1*, available at: http://www.omim.org/entry/590050.

[44] Online Mendelian Inheritance in Man (2012) *256000: Leigh syndrome; LS*, available at: http://www.omim.org/entry/256000.

[45] Online Mendelian Inheritance in Man (2010) *590060: Transfer RNA, mitochondrial, lysine; MTTK*, available at: http://omim.org/entry/590060.

[46] See: Human Fertilisation and Embryology Authority (2009) *HFEA Research Licence Committee meeting*, available at: http://guide.hfea.gov.uk/guide/ShowPDF.aspx?ID=3825.. In 2012, a decision on an application from the same group requesting a licence to perform PGD for two other named conditions was deferred pending the provision of further information about the conditions. See: Human Fertilisation and Embryology Authority (2012) *HFEA Licence Committee meeting*, available at: http://guide.hfea.gov.uk/guide/ShowPDF.aspx?ID=4697.

[47] Human Fertilisation and Embryology (HFE) Act 1990 (as amended), schedule 2, paragraph 1ZA(1)(a), available at: http://www.hfea.gov.uk/495.html.

prognosis. The mutant load can change over time with some types of mtDNA mutations, making it extremely difficult to predict how severely symptoms may be experienced in future.

1.38 PGD has therefore been able to provide a reliable diagnosis for only a minority of mtDNA mutations with specific characteristics including where the severity of the disease experienced is closely linked to the level of mutant load in the cells, the mutated mitochondria are uniformly distributed throughout the cells of the body, and the mutant load is likely to remain at a stable level over the person's lifetime.[48] However, a review published in March 2012 has established for the first time that carriers of all heteroplasmic mtDNA mutation types will have a fair chance of having healthy offspring by using PGD, if embryos are transferred with a minimal mutation level. While highlighting several caveats and the prior necessity of factoring in information about the patients concerned, the researchers estimated that in most cases, an 18 per cent mutation level will be associated with a 95 per cent or higher chance of not being affected by mitochondrial disorders. However, not every heteroplasmic woman will produce embryos suitable for transfer according to this model with a mutant load of 18 per cent or less. A woman may only produce embryos at a 'borderline' mutant load of perhaps 20 per cent or 25 per cent, necessitating decisions about embryo transfer which may be greatly influenced by the condition or mutation concerned and by the family's prior reproductive history and personal experience of its impact. Such decisions are likely to also be strongly influenced by the woman or couple''s overall fertility prospects, which in some cases may outweigh their wish to avoid transmitting a genetic condition. However, the researchers note that "it is highly likely based on our experience and that of others that mtDNA carriers generally produce some oocytes below the threshold."[49]

1.39 Although it seems likely that PGD will be able to inform a reliable diagnosis for most heteroplasmic mtDNA mutations, no diagnosis can absolutely guarantee parents that the child will be healthy. Also, even where PGD has been used, future generations are still at risk of developing an inherited mtDNA disorder. Girls born who were identified by PGD as having a low level of mutated mitochondria could go on to have affected children, as they may still have some mutated mitochondria in their eggs.

1.40 PGD will also not help women at the greatest risk of passing on mutated mitochondria: heteroplasmic women with a very high mutant load (who are likely to have symptoms of mitochondrial disorders and may not be able to reproduce), or those with homoplasmy of mutated mitochondria. If all of a woman's embryos are likely to result in children with mitochondrial disorders, egg donation is currently the only way in which she can carry a pregnancy and ensure that her children will be born unaffected.

Prenatal diagnosis (PND)

1.41 PND describes different techniques which sample cells at different stages of pregnancy in order to gather genetic information for testing. They include chorionic villus sampling (CVS), a procedure which is offered between 11 and 14 weeks of pregnancy, where cells are taken from the placenta in order to detect specific abnormalities in the fetus. Amniocentesis is a different technique in which cells are taken from the amniotic fluid (the fluid which surrounds the fetus in the womb). This procedure is offered from around 15 weeks of pregnancy. Both of these invasive procedures involve passing a needle into the woman's body, and so create a small risk of miscarriage, of usually one per cent or lower.[50]

1.42 As with many other prenatal tests, depending on the information that is received, some women and their partners may find the information gathered helpful in preparing for a baby who may or

[48] Bredenoord AL, Pennings G, Smeets HJ, and de Wert G (2008) Dealing with uncertainties: ethics of prenatal diagnosis and preimplantation genetic diagnosis to prevent mitochondrial disorders *Human Reproduction Update* **14**: 83-94.

[49] Hellebrekers D, Wolfe R, Hendrickx A *et al.* (2012) PGD and heteroplasmic mitochondrial DNA point mutations: a systematic review estimating the chance of healthy offspring *Human Reproduction Update* **0**: 1-9.

[50] Amniocentesis and CVS have miscarriage risks of approximately one per cent and two per cent, respectively. See: NHS Choices (2012) *Chorionic villus sampling: complications*, available at: www.nhs.uk/Conditions/Chorionic-Villus-sampling/Pages/Risks.asp.

may not have serious health problems or a limited life expectancy. Others may face a decision about whether to continue with the pregnancy or to seek a termination. In addition to the difficulties faced by any couple facing a decision of whether or not to end a wanted pregnancy because of a potential fetal health problem, decision-making can be especially difficult in the case of mitochondrial DNA mutations because of predictive uncertainties.

1.43 With some kinds of mitochondrial mutations, relatively early prenatal testing such as CVS can be offered to assess the load of mutant mitochondria.[51] In other cases, the degree of certainty of information gained via PND may only be improved if a woman undergoes sequential testing into the third trimester (up to 28-30 weeks pregnant).[52] However, where there is uncertainty of interpretation due to intermediate mutation loads (i.e. mutation loads which are at neither one extreme nor another), this uncertainty will remain regardless of the gestational point at which the sample is taken.

1.44 Where testing in the third trimester is undertaken to improve certainty, and appears determinative of substantial risk of serious health problems to the future child, parents may be face a decision about whether to proceed with the pregnancy. After 24 weeks of pregnancy, referral for termination from two doctors can be difficult to access. In 2010, 147 abortions took place at over 24 weeks' gestation in England and Wales across all of the legal grounds applicable from that gestation up until birth; this was out of a total number of abortions of 189,574 at all gestations on all legal grounds.[53] A choice of abortion method is unlikely to be available after 24 weeks, as only a handful of NHS and charitable centres in England and Wales provide surgical abortion under general anaesthetic. This means that most women ending a pregnancy in the third trimester will need to have an induced labour and deliver the fetus, whether or not this would be the method they would prefer.

1.45 PND may not have any greater predictive power than PGD, and predictive uncertainties may remain after PND has been performed. This could be partly because PGD tests around 12.5 per cent or less of a very early embryo, whereas PND samples a greater number of cells but these are only taken from a limited part of the external embryonic tissue (the developing placenta). Overall, PND may be a less suitable route to diagnosis than PGD, because of difficulties in interpreting the fetal mutant load, especially for the couples most likely to produce the most severely affected children if the heteroplasmic mother uses her own eggs to conceive. These couples currently only have the option of undergoing PGD cycles if they wish to use the woman's egg to have an unaffected child, but this comes with no guarantee of implantation and pregnancy even after successful genetic testing.

1.46 What this means is that only the two emerging cell reconstruction techniques, maternal spindle transfer and pronuclear transfer, would, in theory, offer the opportunity to prevent the transmission of mtDNA disorders to all women who want to use their own eggs to have children. The techniques could be used regardless of the type or severity of mtDNA disorder that the woman could otherwise be likely to pass on.

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[51] Dean NL, Battersby BJ, Ao A *et al.* (2003) Prospect of preimplantation genetic diagnosis for heritable mitochondrial DNA diseases *Molecular Human Reproduction* **9**: 631-8; Poulton J, Kennedy S, Oakeshott P, and Wells D (2009) Preventing transmission of maternally inherited mitochondrial DNA diseases *BMJ* **338**.

[52] Faivre L, Cormier-Daire V, Chretien D *et al.* (2000) Determination of enzyme activities for prenatal diagnosis of respiratory chain deficiency *Prenatal Diagnosis* **20**: 732-7; Steffann J, Gigarel N, Corcos J *et al.* (2007) Stability of the m.8993T→G mtDNA mutation load during human embryofetal development has implications for the feasibility of prenatal diagnosis in NARP syndrome *Journal of Medical Genetics* **44**: 664-9.

[53] See: Department of Health (2011) *Abortion statistics, England and Wales: 2010*, available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_126769, table 9, footnote 2. Termination of pregnancy is only lawful after 24 weeks of gestation where there is a grave threat to health or life or where two doctors agree that there is a substantial risk that if the child were born it would be 'seriously handicapped'. See: s1(1)(d) Abortion Act 1967, available at: http://www.legislation.gov.uk/ukpga/1967/87/section/1.

Chapter 2

Science and medical background to the new techniques

Chapter 2 - Science and medical background to the new techniques

About pronuclear transfer (PNT)

Box 2.1: How would pronuclear transfer (PNT) be done?

The principle of the technique is as follows:

- First, IVF is performed using the intending parents' sperm and egg. After a sperm enters an egg, the fertilised egg contains the separate genetic material of the sperm and that of the egg cell each enclosed in a membrane. These are called the male and female pronuclei. Left to develop, each pronucleus containing the genetic material would later come together in the egg, which is now referred to as a 'zygote'.[54] Ultimately, these form a complete nucleus which would then populate each cell of the embryo as they divide and the embryo develops.
- The embryo also contains the mother's mutated (unhealthy) mitochondria, which originates from the cytoplasm in her egg.
- At one day of development, the parents' embryo is still a single undivided cell. The two pronuclei are removed from the parents' single-celled zygote and retained for transfer. This leaves behind almost all of the mother's affected mitochondria. This enucleated cell is then discarded along with the unhealthy mitochondria it contains.
- The egg of a donor with healthy mitochondria is then fertilised *in vitro* either using the sperm from the intending father, or if not of sufficient quality, donor sperm can be used.
- At the same one-cell stage of development, the two pronuclei made with the donor's egg are removed and discarded.
- The parents' pronuclei are then placed into the second, enucleated zygote. This reconstructed embryo cell now contains the pronuclear DNA from the intending parents, and healthy mitochondria from the donor's egg.
- The intention is then that the reconstructed zygote should continue to develop as an embryo suitable to be transferred into the womb of the intending mother with the aim of establishing a pregnancy unaffected by inherited mitochondrial disorders.

Scientific developments around pronuclear transfer

2.1 Experiments using mice conducted since the 1990s have shown that reconstructed embryos continue to develop after pronuclear transfer. These experiments have suggested the efficacy of PNT as a means of preventing the transmission of a mitochondrial DNA deletion.[55] Although the technique has not yet resulted in a live human birth, attempts have been made to demonstrate feasibility in human embryos. In 2003, it was reported that a research team at Sun Yat-Sen University in Guangzhou, China, had experimented with PNT in human embryos.[56] They transferred reconstructed embryos to the uterus of a woman who was being treated for infertility; this would not have been a lawful procedure in the UK. Five embryos were transferred and the woman became pregnant with triplets. The multiple pregnancy was then selectively reduced to a

[54] At the beginning of the process of fertilisation, the sperm and egg each contribute separate 'pronuclei' within the zygote (one-celled embryo). The genetic material in these will then merge to form the mature nucleus of the fertilised egg. From the two-cell stage of embryonic development onwards, the embryo's cells will contain one nucleus which combines both parents' DNA.

[55] Jenuth JP, Peterson AC, Fu K and Shoubridge EA (1996) Random genetic drift in the female germline explains the rapid segregation of mammalian mitochondrial DNA *Nature Genetics* **14**: 146-51; Meirelles FV, and Smith LC (1997) Mitochondrial genotype segregation in a mouse heteroplasmic lineage produced by embryonic karyoplast transplantation *Genetics* **145**: 445-51; Meirelles FV, and Smith LC (1998) Mitochondrial genotype segregation during preimplantation development in mouse heteroplasmic embryos *Genetics* **148**: 877-84; Sato A, Kono T, Nakada K *et al.* (2005) Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation *Proceedings of the National Academy of Sciences of the United States of America* **102**: 16765-70.

[56] BBC News Online (14 October 2003) *Foetus with three parents created*, available at: http://news.bbc.co.uk/1/hi/health/3189718.stm.

twin pregnancy. Some months later, the woman suffered successive miscarriages, losing both fetuses.

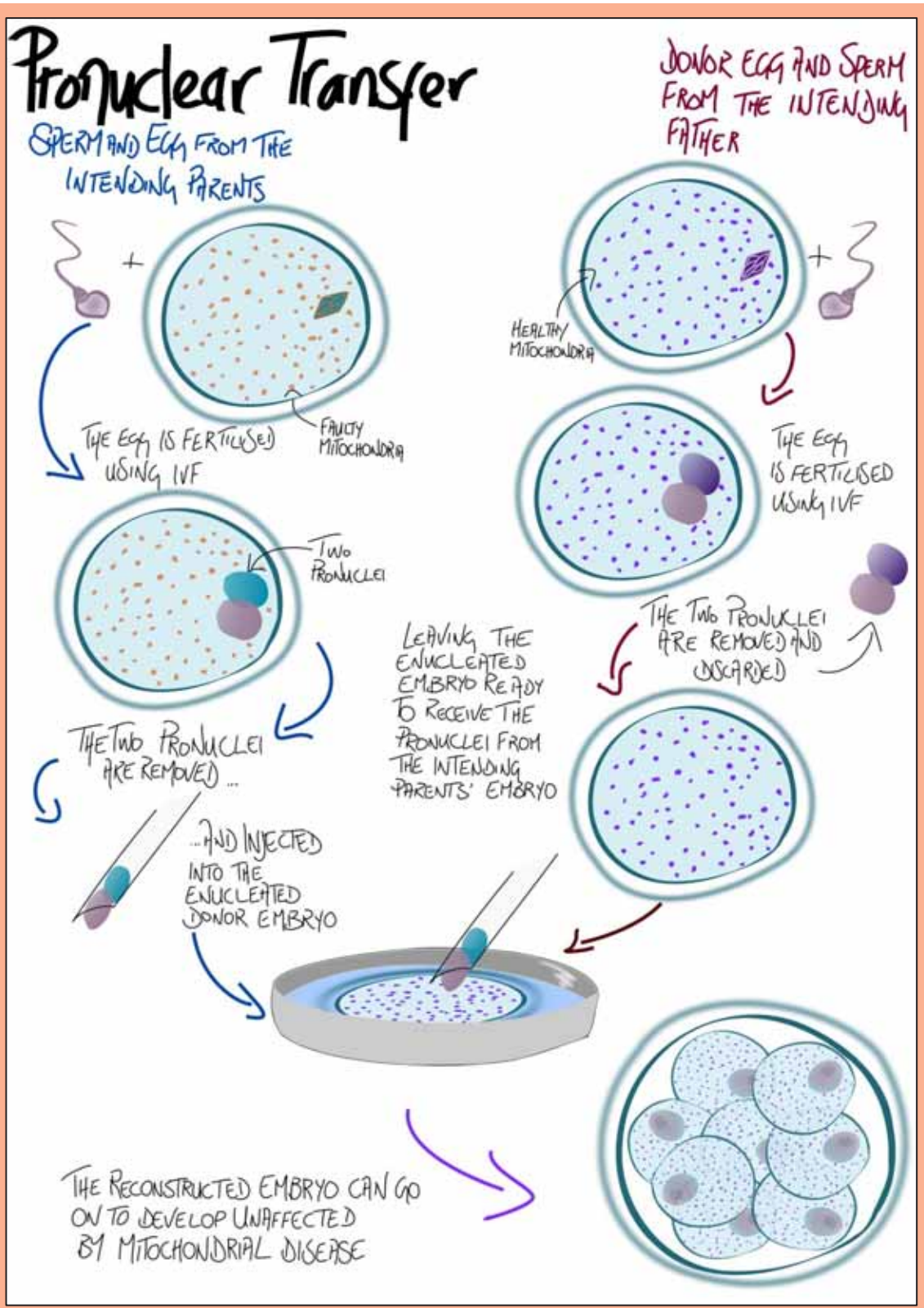

Illustration by Rebecca Kent

2.2 In 2008, researchers from Newcastle University in the UK told a scientific meeting that under an HFEA licence granted in 2005,[57] they had successfully transferred pronuclear DNA between very early (day one) single-celled human embryos (zygotes) which had been donated after being shown to be unsuitable for use in fertility treatments because they contained an abnormal number of pronuclei after fertilisation. After performing the procedure, the Newcastle group grew ten embryos in the lab for five days before arresting their growth so that researchers could analyse them. Although their work had not been published at the time, the results were reported during debates in the House of Lords and calls were made for the technique to be licensed by the HFEA for treatment.[58] Media from all over the world reported on the story, creating headlines about 'three-parent embryos'.[59]

2.3 In April 2010, the Newcastle group published a paper in *Nature* reporting that the transfer of pronuclei obtained from abnormally-fertilised IVF human embryos allowed normal development to the blastocyst (about 100-cell) stage in six to eight days with minimal (on average less than 2 per cent) carry-over of mutated mitochondria, providing proof of concept of the technique in human embryos in a research setting. [60] Some embryos had no detectable carry-over of mtDNA from the mother's egg. The authors of the paper acknowledged that further experiments would still be needed to test the technique in other situations: for example, looking at the outcome of pronuclear transfer when performed on healthy, normally-fertilised embryos, or on embryos created using the eggs of women with a significant level of mutated mitochondria.

About maternal spindle transfer (MST)

Box 2.2: How would maternal spindle transfer (MST) be done?

The principle of the technique is as follows:

- First, assisted reproduction techniques are used to obtain eggs from the ovaries of the intending mother. The cytoplasm of her eggs will contain mutated (unhealthy) mitochondria.
- The maternal chromosomes (nuclear DNA material) in the mother's egg are found towards one side of the egg cell in a spindle-shaped group (hence the name of the technique). This 'spindle' group is removed for transfer to the donor egg. The mother's chromosome-free eggs, which still contain her unhealthy mitochondria, are then discarded.
- Eggs, provided by a donor who has healthy mitochondria, have their spindles removed and discarded leaving behind eggs which contain her healthy mitochondria in their cytoplasm.
- The 'spindles' of chromosomes taken from the mother's eggs are now placed into the enucleated donor eggs.
- The reconstructed eggs now contain nuclear DNA from the mother, and healthy mitochondria from the donor.
- Each egg can then be fertilised with sperm from the intending father or a sperm donor, and the resulting embryo can develop further *in vitro*.
- The intention is then for the one or two reconstructed embryos to be transferred back to the intending mother with the aim of establishing a pregnancy unaffected by inherited mitochondrial disorders.

[57] Human Fertilisation and Embryology Authority (8 September 2005) *HFEA grants licence to Newcastle Centre at LIFE for mitochondrial research*, available at: http://www.hfea.gov.uk/671.html.
[58] House of Lords Hansard (4 February 2008) *c846*, available at: http://www.publications.parliament.uk/pa/ld200708/ldhansrd/text/80204-0002.htm.
[59] Nature News (6 February 2008) *A step towards three-parent babies?*, available at: http://www.nature.com/news/2008/080206/full/news.2008.560.html; BBC News Online (5 February 2008) *Three-parent embryo formed in lab*, available at: http://news.bbc.co.uk/1/hi/health/7227861.stm.
[60] Craven L, Tuppen HA, Greggains GD *et al.* (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease *Nature* **465**: 82-5.

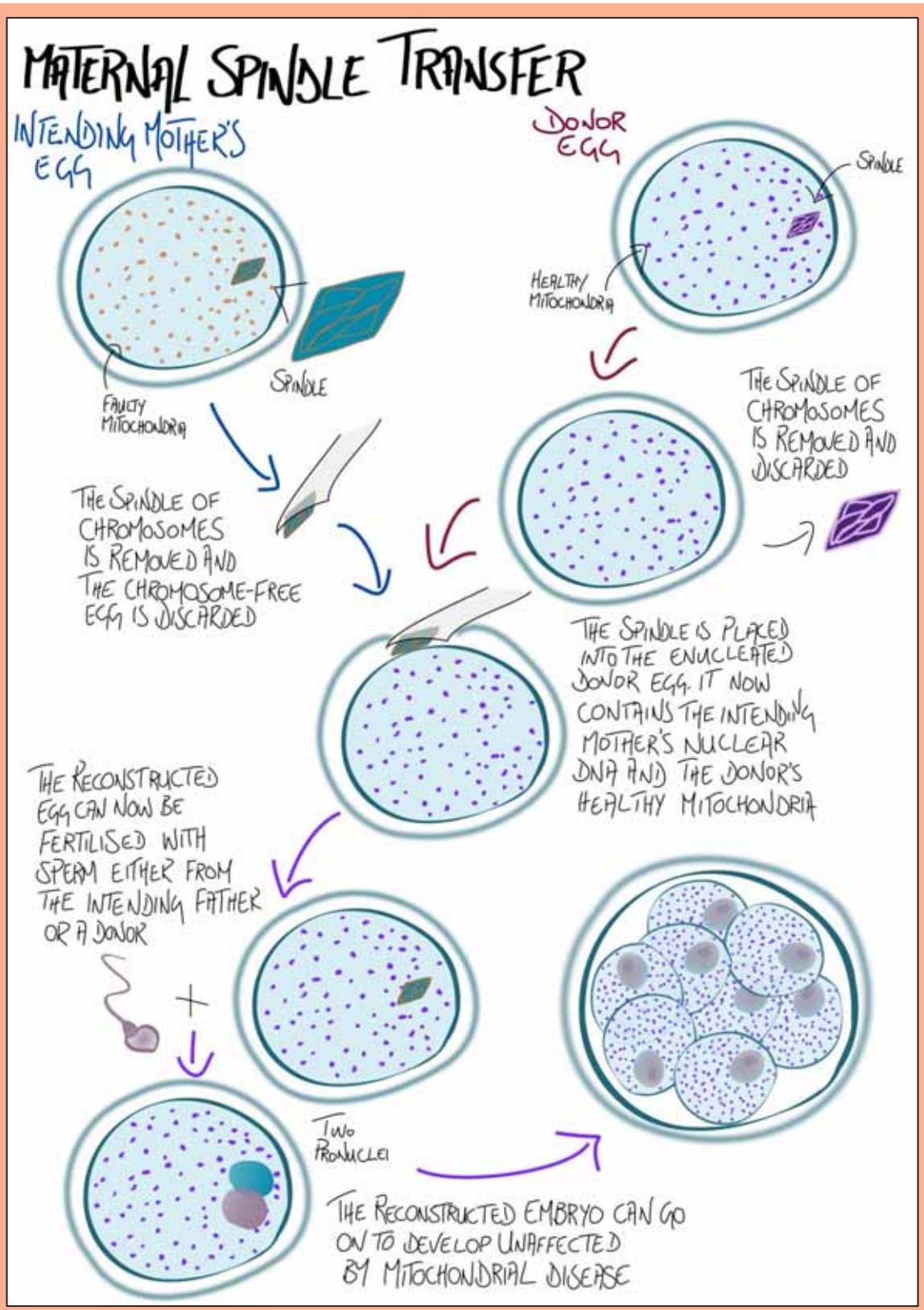

Illustration by Rebecca Kent

Scientific developments around MST

2.4 Maternal spindle transfer (also known as 'metaphase II spindle transfer') is a transfer technique that works on a similar principle to PNT. The main difference between the two techniques is that MST uses two unfertilised eggs to reconstruct an egg with healthy mitochondria that can then be fertilised; in PNT, two early embryos (zygotes) are used to reconstruct an embryo with healthy mitochondria.

2.5 In 2009, US researchers in Oregon announced that they had successfully conducted MST in primates (rhesus macaques) in research seeking to establish proof of principle of the technique.[61] After the MST was carried out, the reconstructed primate eggs were capable of supporting normal fertilisation, and went on to have normal embryo development. Three healthy offspring were produced, which showed no carried-over mitochondria from the egg which had supplied the 'spindle' of chromosomes. Their growth has been monitored monthly and at the age of over two years, no difference was noted between the experimental macaques born following the use of MST and controls.

2.6 Other researchers have pointed to possible gaps in knowledge around the MST technique for example with respect to the identification of any carried-over mitochondria from the spindle donor. [62] In order for the technique to progress towards consideration as a possible treatment in humans, carry-over of mutated mitochondria from the woman providing the spindle for the reconstructed egg would need to be minimised as far as possible.[63]

2.7 In collaboration with the researchers from Oregon, researchers at Newcastle University are currently testing the MST technique on human eggs, the results of which have yet to be published.

Distinguishing PNT and MST from other germline techniques

2.8 It is important to note that pronuclear transfer or maternal spindle transfer should not be confused with other *in vitro* techniques with germline effects which are also not lawful in the UK, such as cytoplasmic transfer or human reproductive cloning.

Cytoplasmic transfer

Box 2.3: How is cytoplasmic transfer (CT) done?

- First, assisted reproduction techniques are used to obtain eggs from the intending mother's ovaries.
- The same techniques are used to get eggs from a healthy donor.
- Cytoplasm is extracted from a healthy donated egg and injected into the egg of the recipient intending mother. (Nothing has been removed from the mother's egg, nor otherwise altered).
- The egg now contains some cytoplasm with mitochondria from the donor added to the original contents of the mother's egg: her mitochondria and nuclear DNA.

This egg can then be fertilised with sperm from the intending father or a donor as necessary, and the resulting embryo then transferred back to the mother. The aim of the technique is to enable infertile women to carry a pregnancy.

[61] Tachibana M, Sparman M, Sritanaudomchai H *et al*. (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells *Nature* **461**: 367-72.
[62] St John J, and Campbell K (2010) The battle to prevent the transmission of mitochondrial DNA disease: Is karyoplast transfer the answer? *Gene Therapy* **17**: 147-9.
[63] Spikings EC, Alderson J, and John JCS (2006) Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer *Human Reproduction Update* **12**: 401-15.

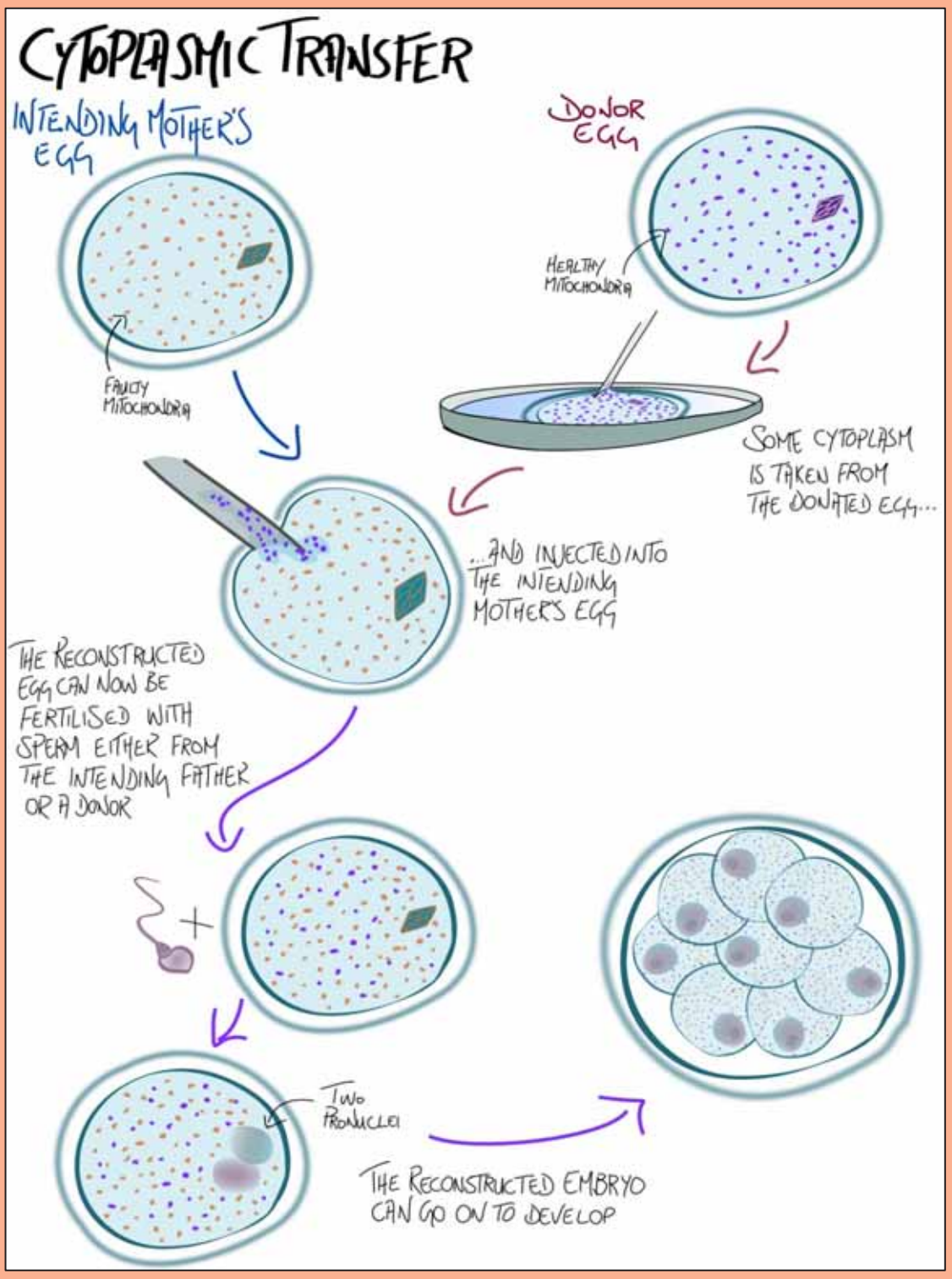

Illustration by Rebecca Kent

2.9 Cytoplasmic transfer (CT), also known as 'ooplasmic transfer', is a technique related to maternal spindle transfer only insofar as it also manipulates unfertilised eggs. CT has been speculatively proposed as a possible option for the prevention of transmission of mitochondrial disorders, but

is not currently performed for this purpose as far as we are aware. CT is used outside the UK in IVF treatment, aimed at 'rejuvenating' the eggs of women with problems in conceiving because of poor embryo development and recurring implantation failure. However, it is not very clear what problem the technique treats, or how it works to achieve pregnancies. The technique was never licensed by the HFEA for use in the UK and would not be legal to offer in the UK under the HFE Act because it alters an egg before it is transferred to a woman.

2.10 CT involves injecting a small amount of cytoplasm containing healthy mitochondria from a healthy, younger donor's egg into the egg of the recipient woman who has had problems in conceiving. The first baby was reportedly born from CT in the US in 1997, after which a small number of further children were born from CT at the same centre. In announcing the first births, researchers hailed their work as "the first case of human germline genetic modification resulting in normal healthy children".[64] The technique can potentially create germline changes in resulting offspring, because a small amount of the donor's mitochondria may be found in the person's cell cytoplasm as well as their mother's mitochondria, although this was not shown to occur in every documented case. The presence of donor mitochondria was detected in the cells of two out of 15 children at one year of age.[65] People who carry mitochondria from two sources would then be likely to pass these on to any children they have. This heteroplasmy of different variants of mitochondria has prompted safety concerns.[66]

2.11 Although around 30 babies worldwide were thought to have been born by CT by 2001, CT has been largely discredited in the scientific community because of safety concerns.[67] While 15 apparently healthy babies were born after CT, two further pregnancies begun using CT were found to be affected by Turner syndrome,[68] which affects females with varying severity.[69] It results in a lack of ovarian development at puberty and in short stature and may be associated with problems of major organs (such as the heart) and with mild learning difficulties. These two incidences of Turner syndrome – which resulted in a miscarriage and a termination of pregnancy – indicate a higher incidence of the disorder than would normally be seen in the general population. However, the very small cohort makes conclusions difficult to draw.

2.12 One of the 15 babies born at the same centre was then diagnosed at 18 months with pervasive developmental disorder (PDD), a spectrum of conditions which include autism-related diagnoses.[70] Despite this, longer term follow-up of the children born does not appear to have been published, and no central register of US births after the technique has been established.

2.13 In 2001, after problems that had been linked to the CT technique were published, the US Food and Drug Administration (FDA) asserted their regulatory authority over the procedure, effectively banning it and indicated that further research should be undertaken. However, due to the nature of the legal system in the US and unclear FDA powers to rule on this technique, it is unclear whether offering it as a treatment would be illegal in all parts of the country. There were media

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[64] Barritt JA, Brenner CA, Malter HE, and Cohen J (2001) Mitochondria in human offspring derived from ooplasmic transplantation: brief communication *Human Reproduction* **16**: 513-6.

[65] Brenner C, Barritt J, Willadsen S, and Cohen J (2000) Mitochondrial DNA heteroplasmy after human ooplasmic transplantation *Fertility and Sterility* **74**: 573-8; Barritt JA, Brenner CA, Willadsen S, and Cohen J (2000) Spontaneous and artificial changes in human ooplasmic mitochondria *Human Reproduction* **15**: 207-17; Barritt JA, Brenner CA, Malter HE, and Cohen J (2001) Mitochondria in human offspring derived from ooplasmic transplantation: brief communication *Human Reproduction* **16**: 513-6.

[66] Brenner C, Barritt J, Willadsen S, and Cohen J (2000) Mitochondrial DNA heteroplasmy after human ooplasmic transplantation *Fertility and Sterility* **74**: 573-8.

[67] Barritt JA, Brenner CA, Malter HE, and Cohen J (2001) Mitochondria in human offspring derived from ooplasmic transplantation: brief communication *Human Reproduction* **16**: 513-6.

[68] Barritt JA, Brenner CA, Willadsen S, and Cohen J (2000) Spontaneous and artificial changes in human ooplasmic mitochondria *Human Reproduction* **15**: 207-17; Barritt JA, Brenner CA, Malter HE, and Cohen J (2001) Rebuttal: interooplasmic transfers in humans *Reproductive BioMedicine Online* **3**: 47-8.

[69] Turner syndrome results in a lack of ovarian development at puberty and short stature, and may be associated with problems in the major organs, and with mild learning difficulties. See: NHS Choices (2011) *Turner syndrome: symptoms*, available at: http://www.nhs.uk/Conditions/Turners-syndrome/Pages/Symptoms.aspx.

[70] Barritt JA, Brenner CA, Willadsen S, and Cohen J (2000) Spontaneous and artificial changes in human ooplasmic mitochondria *Human Reproduction* **15**: 207-17; Barritt JA, Brenner CA, Malter HE, and Cohen J (2001) Rebuttal: interooplasmic transfers in humans *Reproductive BioMedicine Online* **3**: 47-8.

reports of US couples travelling abroad to seek CT after the ban however, including the parents of a child who had been born following CT.[71] Indeed, at present, CT is offered with IVF in many countries. For example, in 2011, reports from Chennai, India noted the births of healthy twins after CT, which were reportedly the "first in Asia",[72] although this may not be the case. In 2012, commercial websites have listed clinics offering CT in India, North Cyprus, Ukraine, Armenia, Georgia, Israel, Turkey, Thailand, Singapore, Germany and Austria.[73]

2.14 Given the reported problems with the technique, it seems unlikely that at the present time, the research community will investigate CT as a means of preventing the transmission of inherited mitochondrial disorders.[74] CT results in eggs where a small amount of healthy donated mitochondria are added to the mother's mitochondria naturally present in the egg. Experiments with the technique in mice suggest that less than a third of total mtDNA is transferred from the donor in CT.[75] The heteroplasmic population of healthy and mutated mitochondria created by CT might still create mitochondrial disorders.

Human reproductive cloning

2.15 When human reproductive cloning is mentioned, many people think of the somatic cell nuclear transfer technique (SCNT), also known as 'somatic cell nuclear replacement', or 'cloning'.

2.16 The SCNT technique, famously used to create Dolly the cloned sheep in 1996 from a mammary gland cell, would not be lawful if carried out with the intention of establishing a human pregnancy in the UK or in most other countries.[76] However, it has been permitted to clone human embryos in the UK under HFEA licence for research purposes. As with all embryos created or used for research in the UK, these embryos are destroyed after 14 days of development from fertilisation.

2.17 The SCNT technique would work by transferring the nucleus of a somatic cell of one person (meaning any cell other than a gamete, or gamete-producing cell) into an enucleated, unfertilised egg. The reconstructed egg would then be artificially stimulated to encourage cell division, intended to produce a viable cloned embryo for transfer to the womb with the aim of establishing a pregnancy. If born, the 'cloned' baby would have identical nuclear genes to the living or dead individual or entity (cell, embryo, animal or person) that had provided the original somatic cell nucleus. The 'clone' would not be entirely genetically identical to its 'original', however, as its mitochondria would come from an enucleated egg, not from the 'original' pre-existing entity. As with pronuclear transfer, SCNT would not be lawful to offer as a method of medical treatment in the UK under the present legislation as it would alter an embryo before transfer.[77]

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[71] CNN.com (17 June 2004) *How far will couples go to conceive?*, available at: http://edition.cnn.com/2004/HEALTH/03/12/infertility.treatment/index.html.

[72] Indiaeveryday.in (21 November 2011) *Woman conceives through cytoplasmic transfer technology*, available at: http://www.indiaeveryday.in/tamilnadu/fullnews-woman-conceives-through-cytoplasmic-transfer-technology-1133-3268707.htm.

[73] Medicaltourism.in (2011) *Cytoplasmic transfer*, available at: http://www.medicaltourism.in/medical-tourism-procedures/ayurvedic-therapies/gynecology-ivf-treatment-female-reproductive-system-and-pregnancy/cytoplasmic-transfer/cytoplasmic-transfer.html; Health-Tourism.com (2012) *Cytoplasmic transfer abroad: medical tourism guide*, available at: http://www.health-tourism.com/cytoplasmic-transfer/.

[74] Brown DT, Herbert M, Lamb VK *et al.* (2006) Transmission of mitochondrial DNA disorders: possibilities for the future *The Lancet* **368**: 87-9.

[75] Thorbum D, and Dahl H (2001) Mitochondrial disorders: genetics, counseling, prenatal diagnosis and reproductive options *American Journal of Medical Genetics*: 106.

[76] Campbell KHS, McWhir J, Ritchie W, and Wilmut I (1996) Sheep cloned by nuclear transfer from a cultured cell line *Nature* **380**: 64-6.

[77] Only 'permitted embryos' (or, where relevant, 'permitted' gametes) may be placed in a woman; the statutory definition of ''permitted embryos'' includes the stipulation that ''no nuclear or mitochondrial DNA of any cell of the embryo has been altered'', see respectively sections 3(2)(a) and 3ZA(4)(b) HFEA 1990, as amended.

2.18 However, if SCNT were ever to be used in human reproductive cloning for any purpose which would create a baby, this would raise a prohibitive combination of safety and effectiveness barriers, legal issues and ethical concerns. It is important to stress that SCNT techniques have not been proposed as a means of preventing transmission of inherited mitochondrial disorders. This technique is not under consideration as a likely method of avoiding mtDNA disorders.

Nuclear transfer

2.19 However, we acknowledge that a different method, nuclear transfer (NT) might, in the future, be a theoretical avenue of research into the avoidance of mitochondrial disorders. NT is a similar technique to SCNT but is crucially different in using a nucleus taken from a pre-existing embryo- not a somatic cell. Unlike SCNT, NT would not create a 'cloned' baby with identical nuclear genes to a living or dead individual that had provided the original somatic cell nucleus.

2.20 If NT was ever performed for research into avoiding mitochondrial disorders, an IVF embryo would be created by the intending mother who carries mutated mitochondria and the intending father (or a sperm donor, if required) via the normal process of sexual reproduction. This embryo would be allowed to develop a little way beyond the one-celled pronuclear zygote stage seen at day one after fertilisation, to 'completed embryo' stage. By about day five after fertilisation, the one-celled embryo would have divided to become a multi-celled blastocyst. To perform NT, a number of its blastomeres (which each contain a nucleus) would be removed. The nucleus of each blastomere would be extracted and transferred into an enucleated egg from a healthy mitochondrial donor. The aim would be to create an embryo with the parent's nucleus and healthy mitochondria from the donor for transfer to the intending mother's womb. However, as is done with IVF in other scenarios, 'spare' embryos would be created in case of failure to develop before transfer to the woman.[78]

2.21 It is clear that NT could create multiple embryos, by placing existing nuclei from with the same nuclear genes from the parent's unique embryo into perhaps many eggs. NT embryos would have identical nuclear genes and probably very similar mitochondrial genes to each other (assuming the same egg donor is used to make all of the embryos).

2.22 It is beyond the remit of this report to undertake an in-depth discussion of NT, however, we note that if NT research were ever undertaken and appeared to offer the prospect of a future treatment, it would be a question for regulators and ethicists as to whether more than one such embryo should be allowed to be used in treatment and if so, under which circumstances. In any case, it seems likely that NT would be less technically straightforward to perform than either PNT or MST in the reconstruction of embryos or eggs for therapeutic purposes. As far as we are aware, the technique has not been proposed as a research project.

2.23 In contrast to SCNT and NT, at no time could two identical embryos ever exist by the use of the pronuclear transfer method (unless an embryo cleaved afterwards to produce identical twins). The PNT technique creates just one unique and original embryo, by cell reconstruction using two embryos. The parents' embryo carrying high levels of mutated mitochondria is destroyed by the removal of its nucleus. The enucleated embryo from a donor with healthy mitochondria is then used to re-house the parents' nucleus, creating a unique embryo which could be viable for transfer.

Box 2.4: How would nuclear transfer (NT) be done?

The principle of this theoretical technique would be as follows:

- First, IVF techniques are used to create an embryo using the intending parents' sperm and egg. After a sperm enters the egg, the pronuclei in the fertilised egg, (the separate nucleus of the sperm and the egg cells), join together to

[78] Brown DT, Herbert M, Lamb VK *et al.* (2006) Transmission of mitochondrial DNA disorders: possibilities for the future *The Lancet* **368**: 87-9; Bredenoord A, Pennings G, and de Wert G (2008) Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues *Human Reproduction Update* **14**: 669-78.

form the nucleus.

- The embryo also contains the mother's mutated (unhealthy) mitochondria, which came from the cytoplasm in her egg.
- A nucleus is taken from one or more of the cells of the embryo for transfer. This leaves behind almost all of the mother's affected mitochondria. This enucleated embryo is then discarded along with the unhealthy mitochondria it contains.
- An egg of a donor with healthy mitochondria is fertilised with sperm *in vitro*.
- At the same stage of development, the nucleus in the embryo made with the donor's egg is removed and discarded.
- The parents' nucleus is then placed into the second, enucleated embryo. This reconstructed embryo now contains the nucleus from the intending parents, and healthy mitochondria from the donor's egg.
- The intention is then that the reconstructed embryo could continue to develop and be transferred back to the intending mother with the aim of establishing a pregnancy unaffected by inherited mitochondrial disorders.

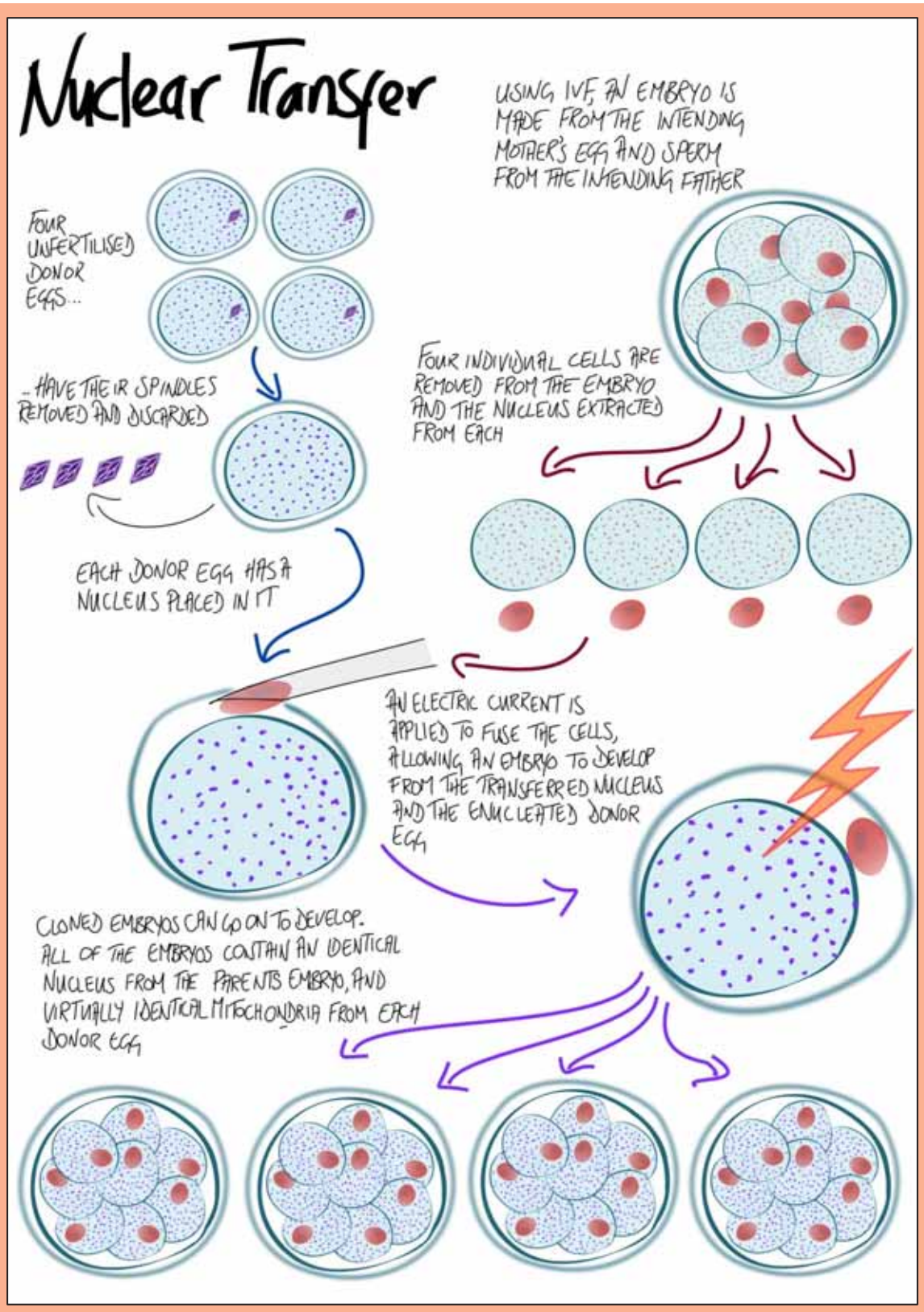

Illustration by Rebecca Kent

Chapter 3

Legal and policy background

Chapter 3 - Legal and policy background

Pronuclear transfer: legal and policy developments

3.1 The Human Fertilisation and Embryology (HFE) Act 1990, (as amended by the Human Fertilisation and Embryology Act 2008), governs prohibitions concerning embryos to be used in licensed research and treatment of patients in the UK. It states that eggs, sperm or embryos which have had alterations made to their nuclear or mitochondrial DNA may not be placed into a woman's body.[79] It is therefore unlawful to offer PNT and MST as treatments in the UK. Reconstructed embryos resulting from either technique would have had the nuclear DNA in their cells altered, and if there had been any mitochondrial carry-over, it would include mtDNA from two sources which could constitute a genetic alteration. Such procedures would not create 'permitted' embryos under the HFE Act 1990 (as amended).

3.2 An embryo is a 'permitted embryo' for transfer to a woman in treatment in the UK only if "no nuclear or mtDNA of any cell of the embryo has been altered".[80] To be a permitted embryo, an embryo must have been "created by the fertilisation of a permitted egg by permitted sperm". An egg is 'permitted' only if it "has been produced by or extracted from the ovaries of a woman, and whose nuclear or mtDNA has not been altered."[81] No cell may have been added to the embryo other than by division of the embryo's own cells. Neither may "genetically modified embryos or embryos created by cloning" be placed into a woman's body.[82]

3.3 The HFE Act was amended in 2008. As the Bill was going through Parliament, there was specific debate about the welfare and prospects of patients with mitochondrial disorders, particularly focusing on the lack of options for affected patients, issues of risk and safety, and questions of identity and parentage should cell reconstructive treatments be permitted.

3.4 The HFE Act (as amended) grants powers to the Secretary of State for Health, if he or she was minded to do so, to create regulations specifically, and only, for the prevention of inherited mitochondrial disorders that would permit the alteration of eggs or embryos as part of treatment. The Act (as amended) also states that regulations may provide that an egg can be a permitted egg, or that an embryo can be a permitted embryo, even though the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease.[83]

3.5 The Act does not, however, specify the method by which a genetic alteration in the 'permitted' embryo or egg would prevent the transmission of mitochondrial disease. Nor does it specify the source of the transmissible mitochondrial disease that the treatment should seek to prevent. Parliamentarians could potentially debate any model of genetic alteration designed to prevent the transmission of either mtDNA or nDNA-linked mitochondrial disorder which had been shown to be acceptably safe and effective.

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[79] Section 3, Human Fertilisation and Embryology Act 1990, as amended. Available at: http://www.legislation.gov.uk/ukpga/2008/22/section/3, See also Human Fertilisation and Embryology Act (as amended) 2008 c. 22 Explanatory Notes: Commentary on Sections: Part 1, 'Section 3: Prohibitions in connection with embryos' paragraphs 28,29, 30. Available at: http://www.legislation.gov.uk/ukpga/2008/22/notes/division/6/1.

[80] Section 3ZA(4)(b) Human Fertilisation and Embryology Act 1990, as amended. Available at: http://www.legislation.gov.uk/ukpga/2008/22/section/3.

[81] Section 3ZA(2)(a) and (b) Human Fertilisation and Embryology Act 1990, as amended. Available at: http://www.legislation.gov.uk/ukpga/2008/22/section/3.

[82] Human Fertilisation and Embryology Act 2008: c.22 – explanatory notes: commentary on sections – part 1 (section 3), available at: http://www.legislation.gov.uk/ukpga/2008/22/notes/division/6/1/3.

[83] Section 3ZA(5) Human Fertilisation and Embryology Act 1990, as amended. In addition, section 26 of the Human Fertilisation and Embryology Act 2008, which inserts a new section 35A into the 1990 Act, makes further provision for ''mitochondrial donation''. See: http://www.legislation.gov.uk/ukpga/2008/22/section/26. See also sections 1(6) and 45A of the Human Fertilisation and Embryology Act 1990, as amended, for further information about forming regulations for the Act. Section 45A, for example, "enable[s] consequential changes to other legislation as a result of amending any of these definitions". See: Human Fertilisation and Embryology Act 2008: c.22 – explanatory notes: commentary on sections – part 1 (section 31), available at: http://origin-www.legislation.gov.uk/ukpga/2008/22/notes/division/6/1/30.

3.6 Such regulations could allow PNT and MST to be offered if they were shown to be safe and effective. Presumably other theoretical methods, that have not yet been developed to prevent the transmission of mitochondrial disorders, might also be debated if similarly demonstrated to be safe and effective in future, whether research is carried out in the UK or elsewhere. These theoretical methods could aim to deal with either mtDNA or nDNA-linked mitochondrial disorders, and so might include embryos altered by germline gene therapies which would act on the nuclear genes, or embryos created by nuclear transfer (NT). However, as the Secretary of State would have to provide draft regulations to be approved by both Houses of Parliament,[84] practical politics would indicate that any treatment method involving germline intervention on nuclear genes, or a NT method would be unlikely to be proposed.[85]

3.7 If Parliament did approve some treatments that would avoid the transmission of inherited mtDNA disorders, however, UK policymakers might need to consider their reasons for only permitting therapies pertaining to mtDNA mutation if, in the future, somewhere in the world a potential germline gene therapy treatment was developed which acted on the nucleus and would prevent mitochondrial disorders caused by genes in the nucleus. Similarly, if potential germline gene therapy treatments were developed that could safely avoid transmission of other serious nuclear genetic disorders, there could be calls to re-examine why the HFE Act stipulates that *only* treatments pertinent to mitochondrial disorders merit exemption from the total ban on the alteration of eggs and embryos before transfer to a woman's body in the UK.

3.8 In February 2011, at the invitation of the Secretary of State for Health, the Human Fertilisation and Embryology Authority (HFEA)[86] established a panel to collate "expert views on the effectiveness and safety of mitochondrial transfer." Their report, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception,* was published in April 2011 and recommended that before PNT and MST could be further considered for use in treatment, specific safety experiments should be undertaken.[87] The report recognised that MST and PNT would theoretically – and uniquely – offer all women with a high level of mitochondrial mutation the opportunity to use their own eggs to carry and give birth to a child unaffected by inherited mitochondrial disorders. The report concluded that "MST and PNT have the potential to be used for all patients with mtDNA disorders, which may make them preferential to PGD in the future. In patients with homoplasmy or high levels of heteroplasmy, [MST and PNT] are the only techniques that would make it possible for them to have a genetically related unaffected child".

3.9 These legal and policy developments may have gained additional impetus because UK scientists are at the forefront of global research into *in vitro* techniques to avoid the transmission of inherited mitochondrial disorders. Scientists in Newcastle have conducted animal and human

[84] See further: Section 45(4) Human Fertilisation and Embryology Act 1990, as amended.

[85] The type of debate most likely to be available to Parliamentarians to discuss delegated legislation such as these regulations, has been criticised as it is limited to about 90 minutes in duration and has been seen as unsuited to the discussion of complex ethical and technical issues. This model of debate would mean that Parliamentarians could not amend government proposals, only accept or reject them. See: House of Commons (2011) *Delegated legislation: brief guide*, available at: http://www.parliament.uk/documents/commons-information-office/Brief-Guides/Delegated-Legislation.pdf. In 2007, the Joint Committee on the Draft HFE Bill noted that the House of Lords Delegated Powers and Regulatory Reform Committee had advised them that: "… the use of an affirmative procedure order to bring additional matters within the scope of an Act is well established." By way of example, the removal of donor anonymity for gamete donors in 2004 was brought about through delegated legislation in this way. They added: "... given that any regulations under clauses 16 and 34 must be passed subject to the affirmative procedure, we are satisfied that this will provide sufficient opportunity for parliamentary scrutiny should genetic modification to prevent serious mitochondrial disease be considered safe in the future." See: Parliament.uk (2007) *Chapter 6: part 2 of the draft bill - amendments of the Human Fertilisation and Embryology Act 1990*, available at: http://www.publications.parliament.uk/pa/jt200607/jtselect/jtembryos/169/16909.htm, paragraph 189.

[86] The HFEA is the independent regulator of embryo research and of most fertility treatments in the UK. See: http://www.hfea.gov.uk/.

[87] Human Fertilisation and Embryology Authority (2012) *Review of scientific methods to avoid mitochondrial disease 2011*, available at: http://www.hfea.gov.uk/6372.html.

embryo research in this area, including successfully performing the first known pronuclear transfers in human embryos.

3.10 The researchers at the Newcastle Fertility Centre at LIFE have held an HFEA research licence permitting them to work on pronuclear transfer techniques using human embryos since 2005.[88]. The application was initially rejected by the HFEA's Research Licence committee on the grounds that the research technique proposed would not be permitted by the HFE Act 1990 (as amended), but these issues were subsequently resolved by an HFEA Appeal Committee and the licence was granted.[89] The Centre, an NHS facility linked with Newcastle University, has since been the chief contributor to this area of research internationally.

Maternal spindle transfer: legal and policy developments

3.11 The same constraints in the HFE Act 1990 apply to the MST technique, as to the PNT technique. MST would only be permitted for use in treatment if Parliament agreed that the meaning of ''permitted eggs'' for treatment should be extended to include "eggs...that have been treated in such a way as specified in regulations to prevent the transmission of serious mitochondrial disease." It should also be noted that what Parliament intended by ''*serious*'' mitochondrial disease in the HFE Act has yet to be established. This distinction does not have a clear medical meaning and many would argue that all mitochondrial disease that produces a need for a clinical intervention would be 'serious' or at least potentially so.

Further legal issues: parenthood

3.12 Some people may feel that the woman donating her mitochondrial genes becomes a 'mother' of the resulting child, or its third biological 'parent'. However, the UK law is framed so that legally it is not possible to recognise two 'mothers'. Instead, a mother and a second female parent can be recognised. We are not aware of any legal recognition of two mothers in any jurisdiction. There is no provision in the HFE Act 2008 for any woman other than the woman who carries and gives birth to a child to be recognised as its legal mother. There is no legal concept of 'genetic motherhood' in the UK, only of gestational motherhood.

3.13 Egg donors have never been recognised as mothers or legal parents. The HFE Act 2008 reiterated this through the inclusion of section 47, headed *Woman not to be other parent merely because of egg donation*. Only women who donate an egg to create a child as part of a 'genetic' or 'full' surrogacy arrangement are regarded legally as the resulting child's mother, but this is because they have given birth and not because of the use of their egg *per se*. This makes it highly unlikely that the law would come to recognise a woman who had donated her mitochondria as either an additional 'mother' or a legal parent of the child, by virtue of the mitochondrial donation alone.

3.14 However, the HFE Act 1990 (as amended) introduced the provision that a child conceived after 6 April 2009 can have two legal parents who are both female, if the couple qualify as joint parents under specific criteria. A co-parenting same-sex couple who meet the criteria would appear on the child's birth certificate as 'mother' (intended to recognise the woman who gave

[88] LIFE is shorthand for The International Centre for Life (ICFL), a ''science village'' in central Newcastle upon Tyne ''where scientists, clinicians, educationalists and business people come together to promote advancement of the life sciences''. See: http://www.life.org.uk/science-village.

[89] Under the Human Fertilisation and Embryology Act 1990, as amended, it is unlawful to create, keep or use an embryo outside the body except under HFEA licence. However, HFEA research licences may authorise the use of embryos for specified purposes, for example "developing treatments for serious disease or other serious medical conditions" if the HFEA is satisfied that the use of embryos is necessary. See: Schedule 2, paragraph 3A(2) Human Fertilisation and Embryology Act 1990, as amended, available at: http://www.legislation.gov.uk/ukpga/2008/22/schedule/2. For details of the Newcastle Centre at LIFE's research application, see: http://www.hfea.gov.uk/1564.html.

birth to the baby) and 'parent'. Where a child has a mother and a second female parent, he or she does not have a legal father.[90]

3.15 There are many different kinds of family arrangements where more than two people take on the role of caring for a child and may be regarded as his or her parents, whether as an ongoing arrangement or consecutively over the course of the child's life. Such roles may be taken on regardless of the protagonists' status as a legal parent, or whether they have a biological link to the child, or live with the child. Examples include (open) adoption, fostering and analogous informal arrangements within families, arrangements between, for example, lesbian couples and a gay man to share parenting of a child they've had together, and in step-parenting after separation or divorce of biological parents where subsequent partners or spouses share parenting of the child. People viewed as a child's parent in a social sense may also include people who have never brought up the child, such as an egg or sperm donor, a surrogate mother, or a parent who for whatever reason is absent from the child's life.

3.16 Where courts are involved in family arrangements, involving more than two parents may be regarded positively. In 2012, a case reached the Court of Appeal regarding contact arrangements for a two-year old child born to a lesbian woman to whom the father had previously been married, in order to allow her to maintain good relations with her family who were opposed to same-sex relationships. She and her female partner had been co-parenting the child, with the father who is also gay, granted limited contact. Lord Justice Thorpe, in the leading judgment, stated that although the lesbian couple desired to bring up the child as a two-parent nuclear family and "it is generally accepted that a child gains by having two parents", that "it does not follow from that that the addition of a third is necessarily disadvantageous."[91]

3.17 Other jurisdictions have moved closer to permitting a child to have three legal parents. In 2005, the New Zealand Law Commission tabled the possibility of legally recognising a child born by donor insemination as having three parents,[92] although there are no known cases of this option being used. In 2007, the Court of Appeal in Ontario, Canada made a declaration of parentage in favour of a lesbian co-mother as the child's third legal parent.[93] The Parliament of New South Wales, Australia is considering whether sperm egg and embryo donors' details could be additionally recorded on birth certificates, where currently only two legal parents of the child can be recorded.[94] The inquiry follows a NSW court ruling to retrospectively remove a sperm donor's name from a child's birth certificate, at the request of a mother and her same-sex partner, who were given permission for their names be on the birth certificate instead. The judge involved reportedly suggested that the law should be reformed to allow donors to be included on birth certification.[95]

3.18 It is to be expected that Government would wish to explore the status of the mitochondrial donor as part of any consultation on regulations around PNT and MST. However, at the time of the debates around the Draft HFE Bill in 2008, secondary information appeared regarding this

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90 Stonewall (2009) Parenthood for same-sex couples, available at: www.stonewall.org.uk/documents/parenthood_for_same_sex_couples_1.pdf; and Human Fertilisation and Embryology Act 2008, available at: http://www.legislation.gov.uk/ukpga/2008/22/part/2/crossheading/cases-in-which-woman-to-be-other-parent.

91 *A v B and* another [2012] EWCA Civ 285, available at: http://www.familylawweek.co.uk/site.aspx?i=ed96467.

92 New Zealand Law Commission (2005) *New issues in legal parenthood: report 88*, available at: http://www.nzlii.org/nz/other/nzlc/report/R88/R88.pdf.

93 *AA v BB & CC* (2007) ONCA 2, available at: http://www.canlii.org/en/on/onca/doc/2007/2007onca2/2007onca2.html.

94 Parliament of New South Wales (2012) Inclusion of donor details on the register of births (Inquiry), available at: http://www.parliament.nsw.gov.au/prod/PARLMENT/Committee.nsf/0/7E4018E851966190CA25792D0017F32F?open&refnavid=CO3_1. See also: BioNews (2012) Australian sperm donors' details could be linked to birth certificates, available at: http://www.bionews.org.uk/page_127654.asp.

95 *BioNews* (2011) Lesbian couple have sperm donor removed from birth certificate, available at: http://www.bionews.org.uk/page_104979.asp; *The Sydney Morning Herald* (2011) Sperm donor name on birth certificate would save pain later, says judge, available at: http://www.smh.com.au/nsw/sperm-donor-name-on-birth-certificate-would-save-pain-later-says-judge-20110817-1iy8w.html.

indicating that if PNT and MST were licensed, Government may intend mitochondrial donors to be treated similarly in regulation to women who donate eggs for reproduction. Egg donors for reproduction have different rights and responsibilities than women providing eggs for research, for example. This includes that people who donated their sperm, eggs or embryos after 1 April 2005 are, by law, mandatorily identifiable to any person born as a result of their donation (once the resulting person reaches the age of 18). For example, the Joint Committee on the Draft HFE Bill stated in 2007: "We suspect that the Government's intention in this respect is that the child should have only two registered parents – those whose nuclear DNA was used to create the embryo – but that the child should be able to discover the identity of the female donor of mitochondrial DNA from the Register of information in the same way as other donor-conceived individuals. This is not entirely clear from the draft Bill and Explanatory Notes, although the Department of Health did provide further information on this point in a memorandum to the House of Lords Delegated Powers and Regulatory Reform Committee. This memorandum suggests that the power in clause 34 might, for example, be used to clarify that the woman who donated the egg with healthy mitochondria could not apply for a parental order on the basis that she only contributed mitochondrial, not nuclear, DNA to the embryo."[96]

3.19 If the same regulatory arrangements were made for mitochondrial donors as for egg donors, and if the people whose conception they helped to bring about were treated in the same way as ''other donor-conceived individuals'', this would mean for example, that mitochondrial donor-conceived people would be able to contact any mitochondrial donor-conceived 'siblings' born with the mitochondria of the same donor.[97] At the age of 18, they would be able to apply for identifying information on the mitochondrial donor, and from there, if they wished, seek to initiate contact with her. Prior to that, they would receive personal but not identifying information about the donor, such as her marital status, ethnicity and the number and gender of her own children, and she would have been encouraged to include a 'goodwill message' that parents could share with the child if they chose to.[98] A restriction would also be placed on the number of families to whom the mitochondrial donor could donate her mitochondria.[99] Mitochondrial donors would be able to find out whether their donation produced children, and the year/s of birth, gender and total number of children born from their donations.[100]

3.20 HFEA regulations that came into force on April 1 2012 mean that egg donors can be compensated a fixed sum of up to £750 per cycle of donation. Mitochondrial donors would presumably be able to be recompensed in the same way as egg donors for both reproduction and research.[101]

3.21 If regulation is proposed by Government and approved by Parliament, the legal status of the mitochondrial donor and the associated regulation may be likely to influence the perception of donors and recipient families as to any social relationships that could be created by the donation, as well as influencing the views of wider society on the matter. The legal status and regulation of mitochondrial donors may also be influential on the number and typical profile of donors who come forward.

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[96] Joint Committee on the Human Tissue and Embryos (Draft) Bill (2007) *Human Tissue and Embryos (Draft) Bill: Volume I – Report*, available at: http://www.publications.parliament.uk/pa/jt200607/jtselect/jtembryos/169/169.pdf. The Department indicated that other parts of the Act that may be modified if ''permitted embryos'' created via mtDNA donation were used in treatment; including: register of (donor) information (section 31); the ability of donor-conceived individuals to request information about their genetic parentage (section 31ZA); the provision of information about donor-conceived genetic siblings (section 31 ZE), and clarification re parental orders (section 54), see further section 35A(2) HFEA 1990, as amended.

[97] See, for example, Human Fertilisation and Embryology Authority (6 April 2010) *HFEA to help donor-conceived siblings contact each* other, available at: http://www.hfea.gov.uk/5838.html.

[98] Human Fertilisation and Embryology Authority (2009) *Your rights and responsibilities as a donor: conceived after 1 April 2005*, available at: http://www.hfea.gov.uk/5554.html.

[99] Human Fertilisation and Embryology Authority (2011) *Chief Executive's letters: CE(11)02 - donation review: preparing for implementation*, available at: http://www.hfea.gov.uk/6855.html.

[100] Human Fertilisation and Embryology Authority (2009) *Your rights and responsibilities as a donor: apply for information*, available at: http://www.hfea.gov.uk/1975.html. http://www.hfea.gov.uk/1975.html.

[101] Human Fertilisation and Embryology Authority (2009) *Egg donation & egg sharing*, available at: http://www.hfea.gov.uk/egg-donation-and-egg-sharing.html; Human Fertilisation and Embryology Authority (2011) *Chief Executive's letters: CE(11)02 - donation review: preparing for implementation*, available at: http://www.hfea.gov.uk/6855.html.

3.22 Perceptions of and views about the relative significance of other kinds of tissue and cell donations that involve DNA vary significantly. This may imply that whilst many people would appreciate that DNA is a part of what's given in a mitochondrial donation, and that the route by which the donor's mitochondria are gathered is the same as for any other egg donation, these factors alone should not indicate that mitochondrial donors ought to be assigned a legal status or model of regulation identical to any pre-existing form of donation.

3.23 The Working Group also noted that if cell reconstruction techniques were licensed for clinical use in the UK, couples from other countries would be likely to come to the UK to use them. At least some of the children born via these techniques would not be born in the UK. For those children, UK law would not cover the legal relationships between themselves, their parents and the mitochondrial donor. This also raises issues in relation to the follow up of the resulting children via a UK register of treatment.

Further legal issues: germline therapies and cloning

3.24 In addition to the UK's prohibitions on germline therapies and reproductive cloning most recently expressed in the HFE Act 2008, international instruments have sought to prohibit such techniques or to create a restrictive climate around them. Such restrictions to any activity which would alter DNA before transfer seem to have been based on safety and ethical concerns about interventions which would act on nuclear DNA, rather than any particular considerations in respect of mitochondrial DNA.

3.25 When reflected in legislation and regulation, this distinction may have the potential to be of possible concern regarding *in vitro* techniques to avoid the transmission of inherited disorders and other future assisted reproductive techniques. Because of prohibitions intended to prevent human reproductive cloning, for example around nuclear transfer, scientists might be restricted to only being able to use possibly less effective alternative techniques in order to develop new therapies.

3.26 UNESCO's International Bioethics Committee (IBC), founded in 1993, drew up the Universal Declaration on Human Genome and Human Rights. This was endorsed by UNESCO in 1997, and by the General Assembly of the United Nations in 1998. This describes the human genome as "the heritage of humanity" (Art 1), and gives the IBC a duty to identify "practices that could be contrary to human dignity, such as germ-line interventions" (Art 24). It states that "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted" (Art 11).[102]

3.27 The Council of Europe's Convention on Human Rights and Biomedicine also published in 1997, which prohibits the creation of embryos for research, also states at Art.13: ''An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.''[103] This is a non-binding Convention, which the UK has not signed, although many European countries have done so. The Convention also includes an "Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings."

[102] UNESCO (1997) *Universal Declaration on the Human Genome and Human Rights*, available at: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html.

[103] Council of Europe (1997) *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine*, available at: http://conventions.coe.int/Treaty/en/Treaties/html/164.htm. The Convention also includes an additional protocol: Council of Europe (1998) *Additional protocol to the convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, on the prohibition of cloning human beings*, available at: http://conventions.coe.int/Treaty/en/Treaties/html/168.htm. This states that "being ''genetically identical'' to another human being means a human being sharing with another the same nuclear gene set" (Article 1(2)).

This stipulates that being "genetically identical" to another human being means ''a human being sharing with another the same nuclear gene set", regardless of the fact that in reproductive cloning the ''original'' and ''clone'' would have different mitochondrial genes, (and in this respect ''clones'' would be less alike than say, identical twins are).[104]

3.28 Some international instruments would not necessarily rule out either nuclear or mitochondrial germline therapies. For example, 1997's UNESCO Declaration on the Responsibilities of the Present Generations Towards Future Generations, Art.6 states: "The human genome, in full respect of the dignity of the human person and human rights, must be protected and biodiversity safeguarded. Scientific and technological progress should not in any way impair or compromise the preservation of the human and other species."[105]

3.29 In 2005, the preamble to UNESCO's Universal Declaration on Bioethics and Human Rights, stated that "based on the freedom of science and research, scientific and technological developments have been, and can be, of great benefit to humankind in increasing, inter alia, life expectancy and improving the quality of life." It continues at Art.16: "The impact of life sciences on future generations, including on their genetic constitution, should be given due regard."[106]

3.30 We feel that it is appropriate to call PNT and MST 'germline therapies' because they would have germline effects. Cell reconstruction via either technique would give a child a different population of (healthy) mtDNA which it would not have received otherwise. The germline of the resulting children is thereby changed. Women, but not men, born from the procedures will give their children copies of the mtDNA sourced from the donor via their eggs, which in turn can be passed on via their daughters' eggs to subsequent generations. We apply the term 'germline therapies' to cell reconstruction techniques for clarity, albeit that in many contexts the label has been applied to techniques which would only act upon nuclear genes.

3.31 We are tasked with considering PNT and MST primarily in this report, but given that devastating mitochondrial disorders can be caused by either nDNA or mtDNA, we feel it is important that the ethical differences between germline therapies that would seek to prevent disorders brought about by either genome are examined. In future, potential treatments involving either source could be developed that are acceptably safe and effective and these should be carefully considered on their merits. Our remit in this report does not extend to a full discussion of the ethics of the different kinds of prospective and theoretical germline therapies.

[104] Council of Europe (1998) *Additional protocol to the convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, on the prohibition of cloning human beings*, available at: http://conventions.coe.int/Treaty/en/Treaties/html/168.htm.

[105] UNESCO (1997) *Declaration on the responsibilities of the present generations towards future generations*, available at: http://www.unesco.org/cpp/uk/declarations/generations.pdf.

[106] UNESCO (2005) *Universal declaration on bioethics and human rights*, available at: http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html.

Chapter 4

Ethical considerations

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Key ethical issues raised by techniques to prevent the transmission of inherited mitochondrial DNA disorders

4.1 Provided that research shows PNT and MST to be effective and acceptably safe as potential treatments, the most obvious ethical reason to permit their use is that they would offer the possibility of preventing the transmission of mitochondrial DNA disorders, which affect some people's health very seriously. Alongside this, they would offer women who carry such disorders, or who are affected by them, the chance to have healthy children who are also genetically related to them.

4.2 Three pressing areas of ethical concern remain, however, which some have argued may potentially override the positive aspects of these techniques:

- that PNT and MST are forms of germline therapy, with the problematic features of germline therapies in general, or that permitting their use would create a 'slippery slope' towards permitting alterations of the nuclear germline.
- that the knowledge regarding the safety of PNT and MST is uncertain and in absolute terms will remain so until several generations of people have been born from the procedure. Permitting their use creates the potential for harm to future persons.
- that a person born with three genetic contributors might have a conflicted or confused self-image, and perhaps conflicted or confused perceptions of the social roles of others in relation to themselves, as a result of this.

4.3 We will address these issues later in the chapter. Before doing so, however, it is necessary to clarify a number of issues regarding 'identity', for cell reconstruction techniques are often discussed using this language.

Notions of identity

4.4 Personal identity is a highly elastic concept which is used to encompass many different ideas. These include, but are not limited to: how a person sees him or herself, how society sees that person, or how we distinguish between individuals. 'Identity' can be used as a banner under which to justify the inclusion or exclusion of people from different types of groups and as a device in campaigning politics. Some people recognise identity as changing over the course of life, but for others identity is a relatively fixed concept which begins at birth (or before, depending on their view on the status of the fetus and embryo).

4.5 A key area of discussion around proposed therapies for mitochondrial DNA disorders has been whether these treatments might alter, or otherwise affect, the resulting person's identity in ways which might be ethically significant. Some commentators do not recognise any contribution of mtDNA towards identity. An HFEA Appeal Committee stated that mtDNA had "no identity effects" in respect of the licence application by the Newcastle Fertility Centre at LIFE to carry out pronuclear transfer research,[107] and the Medical Research Council and the Wellcome Trust

[107] For further discussion, see: HFEA (2010) R0153: Mitochondrial DNA disorders – is there a way to prevent transmission?, available at: http://www.hfea.gov.uk/1564.html#1652, and the sub-documents *Summary of how the HFEA made its decision to license this project of research*, available at: http://www.hfea.gov.uk/docs/R0153_How_the_decision_was_made_to_licence_this_research_project__2_.pdf and HFEA *Mitochondrial DNA disorders: is there a way to prevent transmission*, available at: http://www.hfea.gov.uk/docs/R0153_Extended_Summary_Mitochondrial_DNA_LIFE.pdf. See also for further background on the appeal: HFEA (2005) HFEA grants licence to Newcastle Centre at LIFE for Mitochondrial Research, available at: http://www.hfea.gov.uk/671.html.

responded jointly to our call for evidence to state that: "We do not believe the transfer of mtDNA raises issues around identity, since it does not carry any genetic data associated with the normally accepted characteristics of identity. An analogy could be drawn with replacing the battery in a camera – the brand of the battery does not affect the functioning of the camera."[108]

4.6 The Working Group wished to look at notions of identity in connection with mitochondrial donation, but did not have the remit to cover all of the notions of 'identity' used in discussion of socio-genetic issues. However, it seemed helpful to distinguish at least four ways in which 'identity' is commonly used in discussion of this area.

Self-conception

4.7 First, there is the notion of 'identity' that relates to an individual's self-conception, also understood as one's self-interpretation or self-understanding. As one contributor outlined to our Working Group, this could include "... who you think you are, which is to do with how you experience yourself – and that in turn is partly about your embodied, experienced reality and partly about what other people tell you, implicitly or explicitly, you are. This can be called intersubjective personal identity, as distinct from social identity which is more about what kinds of social positions or roles an individual has, or about family lineages and kinship."[109]

4.8 *S*elf-conception could also involve consciously affiliating oneself with a larger social grouping – adopting a religious or ethnic identity, for example. This sense of identity often points to similarities with others who share it and to dissimilarities with others who do not, making it a useful social or political focus of coalescence.

4.9 Cell reconstruction techniques might impact on self-conception in at least two ways. Firstly, the techniques aim to prevent an inherited disorder from being passed on. Possessing a disorder or an impairment can sometimes be a key element contributing to an individual's self-conception. Thus it follows that the techniques in question (if successful) will be likely to give rise to an individual born with a different self-conception, compared to an individual who could have developed a mitochondrial DNA disorder, had a cell reconstruction therapy not been used.

4.10 Secondly, people who have been made aware that they were born via cell reconstruction therapies may form a self-conception specifically related to their view of themselves as the product of a particular variant of donor-assisted conception. The key question here is whether this self-conception is likely to be ambiguous, conflicted, or otherwise troubling for them. We will address this later in the chapter.

Qualitative identity

4.11 A second notion of identity relates to what we might think of as 'qualitative identity'. To change some aspect of a person is to alter their qualitative identity. This implies nothing ethically troubling *per se.* Many such changes will be trivial, such as having a haircut or losing some weight. Other qualitative changes might be more significant, such as reduced mobility arising from an accident or illness, for example.

4.12 Many medical treatments and interventions are intended to improve a person's health (and thus will change their qualitative identity) compared to their identity had the treatment or intervention not been used. The important ethical question is whether changing the person's qualitative identity is likely to adversely affect them. These issues are addressed later in this chapter with reference to some of the potential adverse effects of cell reconstruction techniques. The notion

[108] Response by the Medical Research Council and the Wellcome Trust to the Working Group's call for evidence.
[109] Oral presentation by Dr Jackie Leach Scully, Professor of Social Ethics and Bioethics at Newcastle University, to a fact-finding meeting of the Working Group in London, 17 February 2012.

of qualitative identity can mean that if (let's say) two people or two objects are exactly alike, they may share the same qualitative identity. The fictional characters of Tweedledum and Tweedledee are qualitatively identical, for example.[110]

Numerical identity

4.13 A third notion of identity might be 'numerical identity'. Tweedledum and Tweedledee may be qualitatively identical but as two separate and distinct individuals, they have separate numerical identities. Qualitative identity can change without affecting numerical identity: for example, the person whose mobility has been affected by an accident or illness clearly remains numerically the same person.[111] A shared numerical identity would mean that (let's say) two people or objects have different qualities, but they are at the same time one and the same person or object.

4.14 Some medical interventions may be significant enough to permit the conclusion that an altogether different and distinct person has come to exist (altering the numerical identity of the resulting person) rather than the intervention altering an aspect of the person (altering their qualitative identity). Suppose we take Parfit's example of a woman who uses contraception to delay having her first baby by several years.[112] The child she eventually gives birth to was made by different gametes, has a different environment in early childhood and goes to a different school, compared with a child that would have existed had she conceived earlier. Many people would view these differences as significant enough to say that the woman's use of contraception has altered the numerical identity of her first baby. If we accept this, it does not follow that preconceptual interventions are ethically wrong on the grounds that they are numerically identity-altering. The mother cannot be faulted for choosing to delay conception.

4.15 Other preconceptual or prenatal interventions relating to the prevention of serious ill health or impairment could also be seen as numerically identity-altering and as unobjectionable in that respect. In the UK, for example, women who are planning to become pregnant are encouraged to take folic acid supplements to reduce the chance of their future child having spina bifida.[113] It might be argued that folic acid supplements are numerically identity-affecting, as the effects of spina bifida in its most serious forms are likely to be significant enough to say that a different and distinct person comes to exist when the condition has been prevented.

4.16 If a couple uses PGD to inform the selection of a particular embryo for transfer to the woman in the hopes of establishing a pregnancy, this action affects the numerical identity of the resulting child, because one embryo has been selected from amongst others. By contrast, where a technique alters or 'reconstructs' a particular egg or an embryo rather than selecting between individual embryos, it may be less clear whether this intervention should be viewed as likely to change an aspect of the same future person (affecting their qualitative identity), or likely to result in a different future individual than would otherwise have been born, to the extent that we can say their numerical identity has been changed.

4.17 Bioethicist Annelien Bredenoord has argued that: "a germ-line modification will at least affect the qualitative identity of the future person. [...] Even if mtDNA only has a basic cellular function, then it is still meaningful to say that germ-line modification of the mtDNA is likely to change the (qualitative) identity of the future person. After all a person without a mtDNA disease will have a

[110] Carroll L (1871) Through *the Looking-Glass, and What Alice Found There*, available at http://www.gutenberg.org/ebooks/12.
[111] Bredenoord A (2010) *Ethics at the interface of reproductive medicine and genetic technology: the case of mitochondrial disorders*, available at: http://arno.unimaas.nl/show.cgi?fid=20139, p124.
[112] This example is discussed in Parfit D (1984) *Reasons and Persons* (Oxford: Oxford University Press).
[113] Lewens T (2004) What is Genethics? *Journal of Medical Ethics* 30: 326-328; Lewens, T (2009) Enhancement and Human Nature: The Case of Sandel *Journal of Medical Ethics* 35: 354-356.

different phenotype, a different life experience, a different biography and perhaps also a different character."[114]

4.18 The Working Group felt that it could also be arguable that when a couple uses either maternal spindle or pronuclear transfer techniques this changes the numerical identity of the resulting child, compared to the child they would have had without making such an intervention. This was because if the technique were successful, the inclusion of a donor's mitochondrial genes and minimisation of the proportion of maternal mitochondrial genes could make such a very significant difference to the resulting person's life that they could be said to make them 'a different person'. If the technique allowed the resulting person to avoid developing a possibly life-limiting mitochondrial DNA disorder, this would have a range of effects on them which encompass several different notions of identity, including having a different mitochondrial genome than they would otherwise have had, and permitting them very different life choices and experiences.

4.19 Whether PNT and MST are accepted to create either a numerically identity-altering effect, or a qualitative identity-altering effect, the Working Group concluded that of themselves, no further conclusion about the ethical status of these interventions follows by accepting that they have such effects. Many other medical interventions, whether they involve genetic materials or not, are 'identity-altering' according to a variety of notions of identity, so maternal spindle transfer and pronuclear transfer would not be exceptional in this.

Genetic identity

4.20 The idea of a 'genetic identity' seems to have gained ground in the last century. Today many people are aware of genetics and have an interest in ideas of what our genes might mean for our lives. For many of us these views will not go beyond an interest in observing heritable traits and characteristics, for example, but for some people genetic testing has allowed them to take on a sense of identity that is very important to them. For example this could be related to their possession of a distinctive genetic trait.

4.21 These developments have coincided with an increased scientific knowledge of genetics and genetic testing and the introduction of assisted reproductive technologies and their increasing social normalisation. At the same time, there is a greater visibility of family structures which are not novel, but may still be regarded by some as 'non-traditional'. These would include separation or divorce and the formation of subsequent families, and parenting by same-sex partners. Some ARTs and some 'non-traditional' family arrangements permit (or may necessitate) distinctions to be made between the genetic, gestational and social contributors towards the creation and upbringing of children. Taken together, the factors above could make it easier for some people to conceptualise the possession of a personal 'genetic identity', as distinct from other notions of identity. The Working Group discussed, however, that the notion of genetic identity is used to encompass many different things and as such its coherency can be contested.

4.22 For some people the possession of a 'complete' genetic identity is a powerful concept, a form of knowledge that is necessary in order to live one's life in a satisfactory way. If this knowledge is withheld, for example in donor conception for reproduction where a gamete donor is not identifiable, some people have argued that this is a painful loss in their lives, perhaps because they would like the opportunity to seek contact with the person(s) who provided the sperm or the eggs by which they were conceived. This is illustrated in a recent newspaper comment piece about the legal struggle of Canadian donor-conceived people around donor anonymity. "Olivia Pratten and Shelley Deacon are the issue of anonymous sperm donors. Both have been

[114] Bredenoord A (2010) Ethics at the interface of reproductive medicine and genetic technology: the case of mitochondrial disorders, available at: http://arno.unimaas.nl/show.cgi?fid=20139, p125.

seeking information about their hidden bio-history for years. Last year the British Columbia Supreme Court granted the women access to their bio-files, and in the process, struck down as unconstitutional provisions of the Adoption Act. The government was given six months to amend the act, and now the government is in court seeking to overturn that ruling [... but] why should these young women – and all the other donor children they represent – go through life suffering the torment of knowing only half their genetic identity?"[115]

4.23 The Working Group feels that it is arguable that what is being sought here may not be best described as 'genetic identity', as it is more about seeking social information or a narrative related to a specific, limited element of the women's biological origins. The women do not seek genetic information about themselves, as they could have obtained this via genetic testing. The information sought is about the life and perhaps the family background of the man who donated the sperm which contributed half of their nuclear genetic makeup. Social contact with the donor might add to the women's knowledge of their own genetic makeup in some ways – for example if he disclosed a genetic trait hitherto unmentioned – but is otherwise unlikely to elicit genetic information aside from perhaps permitting the observation of shared physical traits or characteristics. While an interest in being able to access this information or to experience contact may be understandable (and is an extremely strong desire for some people), it seems debatable as to whether the information gained is best described as finally affording a donor-conceived person a full 'genetic identity'. The social or genealogical information sought appears to provide increased social information about the contributors to one's origins and so perhaps augments an aspect of one's sense of identity, but not in a specifically 'genetic' sense.

4.24 'Genetic identity' is also insufficient as a sole means of discerning personal identity. Although variations in the nuclear (but not mitochondrial) genome can be used to identify most people as unique individuals compared to others, this information alone is not enough to establish individual identity. A literal view of genetic identity would for example see monozygotic ('identical') twins described as being the same person, and a baby being regarded as the same as his or her placenta. Genetic information can identify individuals from amongst other individuals, if put together with other kinds of information, but in total this information does not reveal anything about that individual's sense of 'genetic identity', in the self-conceived sense of 'who they think they are'.

4.25 The use of cell reconstruction techniques could be seen to affect the (mitochondrial) genetic identity of the resulting child, in that the techniques would enable a person to be born who is genetically distinct from the person who might have been naturally conceived by his or her parents. The same likelihood of identity effects could be expected for therapeutic interventions in the nuclear genome. Depending on the egg donor used in PNT or MST, the procedure may introduce only a very small change to the resulting child's mitochondrial genetic identity. The mitochondria of donors genetically related to the woman with mitochondrial mutations will be very similar or in many cases identical to any non-mutated part of the woman's mitochondrial population. This would mean that if a close maternal relative's mitochondria was used in cell reconstruction, the child would receive what was effectively 'the same' mitochondria as they would have received from their mother, but minus the mutated mitochondria. The Working Group felt that the fact that the child's genetic profile is changed by a therapeutic intervention, cannot be assumed to affect (or to negatively affect) their conception of 'who they are', although it may have this effect. The Working Group agreed that a key ethical test connected to identity is whether a proposed therapy safeguards the resulting child's right to an 'open future', as compared to not performing the therapy.[116] If it were concluded in a particular case that creating

[115] *National Post* (15 February 2012) Sperm-donor children have a right to know their identity, available at: http://fullcomment.nationalpost.com/2012/02/15/barbara-kay-sperm-donor-children-have-a-right-to-know-their-identity/.

[116] Bredenoord A, Dondorp W, Pennings G, and De Wert G (2011) Ethics of modifying the mitochondrial genome *Journal of Medical Ethics* **37**: 97-100.

a child who is less likely to develop a serious genetic disease fulfils this criterion, on this view offering such a therapy may be acceptable.[117]

4.26 Bioethicist Annelien Bredenoord has critiqued any ethically significant distinction that might be attempted to be drawn using notions of identity, between nuclear DNA and mitochondrial DNA interventions aimed at preventing inherited mitochondrial disorders. She notes: "...the dichotomy between modification of the nuclear DNA and modification of the mtDNA is untenable from this perspective: no matter whether one modifies a (pathogenic) nuclear gene or a (pathogenic) mitochondrial gene, the identity of the future person will be changed."[118]

4.27 The Working Group is similarly sceptical of locating any distinction about the ethical acceptability of interventions on different genomes in notions of identity, because developing a possibly life-limiting disorder (or not) can make such a significant difference to the life of the future person. The Group observed that mitochondrial disorders (or their absence) can affect multiple aspects of identity including self-conception (which may include notions of 'genetic identity'), one's bodily identity and social identity, regardless of which genome contains the causative mutations.

Therapies with germline effects

4.28 Not all gene therapies which aim to solve genetic problems are 'germline' gene therapies. 'Gene therapy' is usually taken to refer to those therapies which, whilst improving or curing diseases caused by a genetic fault, are not inherited, as they do not usually affect the person's egg or sperm cells. The therapy acts only to benefit the person concerned, and the genetic changes made cannot be passed on to future generations. Gene therapies currently licensed in the UK make no changes to the germline via either the nuclear or mitochondrial genes.

4.29 'Germline' gene therapies are usually thought of as treatments which make changes to the nuclear or mitochondrial genes in the eggs or sperm of existing people (or the cells from which eggs or sperm will develop), or which use *in vitro* techniques to make changes to very early embryos. Altering the germline could be the primary purpose for offering a therapeutic treatment, or could be a side effect of a therapeutic treatment. These interventions would mean that the resulting person's offspring may grow up to have different traits from those which would have developed, had the gametes (or early embryo) not been altered. Such changes will persist in the genes passed on to the offspring's own children, and so on down the generations.

4.30 PNT and MST techniques potentially allow children to be born with normal cellular energy production, because healthy donated mitochondrial DNA would populate their cells. As a consequence of this intervention, the resulting child's sperm or egg cells (their 'germline') would also develop using the donor's mitochondria. Copies of the mitochondria that came from the donor would thus be passed on via their eggs by any females born after such treatments. Males born after PNT and MST would also have the donor's mitochondria in their cells including in their sperm cells, but as mitochondria are maternally inherited, their children would not inherit mitochondria (nor any associated disorders) from them.

4.31 Commentators disagree as to whether PNT and MST should be regarded as germline therapies. Some argue that germline modification of the mitochondrial genome is germline therapy, and also that in terms of effects on the identity of a future person it is not substantively different from other germline therapies which act on the nuclear genome: "Recent preclinical studies have shown the feasibility of specific variants of nuclear transfer to prevent

[117] Feinberg J (1980) The child's right to an open future, in *Whose child? Children's rights, parental authority and state power*, Aiken W (Editor) (Totowa, New Jersey: Rowman and Littlefield).
[118] Bredenoord A (2010) Ethics at the interface of reproductive medicine and genetic technology: the case of mitochondrial disorders, available at: http://arno.unimaas.nl/show.cgi?fid=20139, p125.

mitochondrial DNA disorders. [These] could be a valuable reproductive option for carriers of mitochondrial mutations. A clinical application ... would entail germ-line modification, more specifically a germ-line modification of the mitochondrial genome. [...] Modification of the mtDNA is not substantively different from modification of the nuclear DNA in terms of its effects on the identity of the future person... the moral acceptability of germ-line modification does not depend on whether it alters the identity of the future child – all germ-line modifications do – but on whether it safeguards the child's right to an open future." [119]

4.32 Others do not regard PNT and MST as germline therapies because they do not act on the nucleus (or at least, they are not thought to do so). For example, a group of British researchers and academics including some who have researched pronuclear transfer in human embryos have argued that: "Germline gene therapy is a term used for modifying genes in the nuclear genome at the beginning of development with the intention of changing the organism in a specific way and for potentially transmitting this change to subsequent progeny. Due to the complexity of the nuclear genome, there are risks associated with modifying it, thus only gene therapy that avoids the germline is currently permitted. Replacing diseased mitochondria with healthy ones is an inherently less complicated procedure. No genome is being modified. Whole mitochondria are being replaced. It is true that once normal mitochondria are in place, the subsequent generations will have normal mitochondria too – hardly a bad thing."[120]

4.33 Similarly, in a Lords debate on the Human Fertilisation and Embryology Bill in 2007, Lord Walton said of the techniques: "People have asked whether this is the same as germ-line gene therapy, a term used for modifying a gene in the nuclear genome at the beginning of development. It is not germ-line therapy, because mitochondrial genomes are not being modified; they are simply being replaced."[121] In a Public Bill Committee discussion on the same Bill in 2008, Dr Evan Harris MP said: "...it is possible to change the DNA in mitochondria without its being considered germ-line gene therapy or germ-line gene engineering, because we restrict that to nuclear DNA."

4.34 It has also been questioned whether the transmission of mitochondria and mitochondrial DNA can be seen as a 'germline' process in the strictest sense as it is a cytoplasmic transmission which also occurs in any somatic cell division. Some might argue therefore that this transmission should be regarded as a "somatic" process whether it happens *in vivo*, or *in vitro* and thus as a very early form of somatic gene therapy, rather than a germline therapy, although this is not a view which the Working Group adopted.

4.35 In spite of the separability of alterations to nuclear and mitochondrial genes which some commentators argue for, the Working Group will however refer to the techniques of PNT and MST as 'germline therapies' because they introduce a change that is incorporated into the (mitochondrial) genes of the resulting people, and so will be incorporated into the germline that they will go on to develop. This terminology seems appropriate because before the cell reconstruction procedure was performed and the relevant parts of the mother's and donor's egg or embryo combined, the person that would have originally resulted from their mother's egg or embryo had it been left unchanged would have had a different genetic makeup (and thus, a different germline). We refer to the techniques of PNT and MST as 'germline therapies' while acknowledging that some changes to the mitochondrial genes have germline effects that are different from the germline effects of changes to nuclear genes. Differences include that PNT and MST are not intended or known to affect nuclear genes; they aim to make no changes to

[119] Bredenoord AL, Dondorp W, Pennings G and De Wert G (2011) Ethics of modifying the mitochondrial genome *Journal of Medical Ethics* **37**:97-100.

[120] North East England Stem Cell Institute (2008*) Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation*, available at: http://www.nesci.ac.uk/assets/docs/NESCIbriefon2008HFEbill-MitochondrialTransplants-Vers01-6.pdf, p4.

[121] House of Lords Hansard (3 December 2007): *c1506*, available at: http://www.parliament.the-stationery office.co.uk/pa/ld200708/ldhansrd/text/71203-0004.htm. See also the comments of Evan Harris MP: House of Commons Hansard (3 June 2008) *c22*, available at: http://www.publications.parliament.uk/pa/cm200708/cmpublic/human/080603/am/80603s04.htm.

the donor's mitochondria; and only women born from these techniques would be able to pass the changes on to their children.

4.36 PNT and MST, if used in treatment in future, would be the first licensed assisted reproductive techniques to change the mitochondrial germline of the resulting people in the UK. However, nuclear germline side-effects of treatments are not uncommon in existing medical treatments which are not intended *a priori* to make changes to the germline. For example, some types of chemotherapy and radiotherapy have this effect, but are not regarded as germline therapies. In the case of these treatments, uncertainty around the risks of germline change may result in advice to people in the reproductive age range to avoid starting a pregnancy for at least a year after undergoing treatment.

Objections to germline therapies

4.37 A key objection to germline therapies is grounded in a concern that such techniques might create health risks to the resulting child and his or her descendants. As with many assisted reproductive techniques, because germline effects are inherited by future generations, it will not be possible to exhaustively assess the safety of the procedures until several generations have been born using them. This means that the first people to use assisted reproductive techniques with germline effects would need to rely on information gained from animal studies undertaken over several generations and from human embryo research.

4.38 The issue of consent is also raised in respect of all germline therapies, given that no child born from such procedures can have consented to them. However, this issue is common to all reproductive technologies, as well as other prenatal and childhood medical interventions, or interventions on other categories of people who lack capacity.

4.39 The validity of consent has also been raised as a concern where people donate (reproductive) tissue for use in therapies where the effects and outcomes of their donation may not be possible to accurately predict. However other treatments already in use have an uncertain long-term evidence base around any health effects on the resulting children. These include ICSI (intra-cytoplasmic sperm injection) in which an individual sperm is selected and injected into an egg to fertilise it *in vitro*,[122] or PGD (preimplantation genetic diagnosis), in which one or more cells are removed from an early embryo for genetic testing. The same concerns have been raised around egg or ovarian tissue cryopreservation using vitrification, in which a woman stores her own tissue for her use in reproduction at a later date.[123]

4.40 Some commentators assert that the doubts about germline therapy express the single basic worry that it is illegitimate "tampering".[124] This view identifies the key objections to germline therapies in the public debate as: tampering with the "rights of individuals", and with the "social order", or with the "order of nature itself".[125]

4.41 Some believe it is wrong to interfere artificially with the genetic inheritance of future people, including circumstances in which their natural genetic inheritance would cause disease. Leaving aside the problems of trying to ascribe meaningful rights to individuals who might (or might not)

[122] Braude P, and Rowell P (2003) Assisted conception. II—In vitro fertilisation and intracytoplasmic sperm injection *BMJ* **327**: 852-5.
[123] Human Fertilisation and Embryology Authority (2009) *Freezing and storing eggs*, available at: http://www.hfea.gov.uk/46.html; The Telegraph (16 April 2012) *Women able to delay motherhood through ovary freezing*, available at: http://www.telegraph.co.uk/health/healthnews/9206190/Women-able-to-delay-motherhood-through-ovary-freezing.html.
[124] Munson R, and Davis LH (1992) Germ-line gene therapy and the medical imperative *Kennedy Institute of Ethics Journal* **2**: 137.
[125] Munson R, and Davis LH (1992) Germ-line gene therapy and the medical imperative *Kennedy Institute of Ethics Journal* **2**: 137.

exist at a future time, and the concerns that they obviously cannot consent to cell reconstruction, any right of future people to receive a genetic inheritance that has not been 'tampered' with has been questioned.

4.42 One aspect of the 'rights of individuals' argument might concern the broader implications of altering a person's genetic inheritance, which provides many of their uniquely inherited abilities and characteristics. It invokes our duty to safeguard the child's 'right to an open future'.[126] Notwithstanding the academic debate about the precise interpretation and status of this 'right' this is generally taken to highlight the importance of not closing off the child's future options, in order not to restrict his or her ability to author his or her own life. The part of the child's open future dictated by his or her mitochondrial inheritance is, as far as we know, confined to the effective functioning (or not) of the mitochondria. To seek to provide children with healthy mitochondria and thus the likelihood of not going on to experience a debilitating disorder which may shorten their lifespan, is arguably to offer these individuals a more open future than would have been available if interventions with this aim were not used.

4.43 The concern about tampering with the 'social order' may involve fears about a lack of control over new technologies, an age-old concern which has tended to be mitigated to some extent as social norms change regarding technologies or their applications. It may also reflect unease with the prospect of novel techniques being used in future as enhancements, rather than therapies. This concern is not unique to cell reconstructive technologies, as the inequitable distribution of social, financial and physical advantages affect almost every area of life. However, given society's experience with currently available reproductive technologies it seems unlikely that if cell reconstructive techniques were introduced they would have a widespread or deleterious impact upon equality in wider society.

4.44 As with any other relatively rare health condition where only comparatively few individuals may be able to benefit and particularly in a publicly funded health system, consideration will need to be given to whether the resources available within the existing 'social order' would be unduly constrained by the introduction of a new technology.

4.45 As we have previously discussed, alternatives are already available – though these are not exact alternatives to the (theoretical) benefits of PNT and MST. All women who wish to avoid the risks of transmission of mutated mitochondria and who seek to become pregnant can consider using donated eggs. Only a small subset of women in the relatively small section of the population who experience mitochondrial DNA disorders will be unable to use PGD or PND to help them minimise the transmission of mutated mitochondria if they were to use their own eggs.

4.46 Another objection comes from a more intuitive or instinctive position, which is that germline therapies are wrong because they are not 'natural'. Again, to privilege 'natural' genetic inheritance involves accepting the inevitability of genetic problems, which occur naturally. This argument need not have a basis in religious belief, although it may do. This argument may also be applied to general concerns about innovations in medicine or technology.

4.47 In regards to 'tampering with nature', the Working Group is aware that some instinctively find the 'natural' preferable to the 'artificial' in respect of reproduction. It is worth noting, though, that many uncontroversial medical interventions – the provision of kidney dialysis, say, or the allocation of a controlled diet to sufferers of phenylketonuria (PKU) – are highly artificial in the sense that they are the product of intentional technical design.[127] Moreover, even Leon Kass, the former chair of the US President's Council for Bioethics, who is noted for his appeals to the 'wisdom of repugnance' in the domain of reproductive ethics, has pointed out that the mere fact that some process is natural, and in this sense a 'gift', leaves open the question of "which gifts

[126] Feinberg J (1980) The child's right to an open future, in *Whose child? Children's rights, parental authority and state power*, Aiken W (Editor) (Totowa, New Jersey: Rowman and Littlefield).
[127] Lewens T (2009) Enhancement and human nature: the case of Sandel *Journal of Medical Ethics* **35**:354-356.

are to be accepted as is, which are to be improved through use or training, which are to be housebroken through self-command or medication, and which opposed like the plague".[128]

4.48 Given the potential severity of the conditions in question and the lack of treatment options for affected people, it seems reasonable for parents who wish to have a genetically-related child to be able to seek techniques to prevent as far as possible the transmission of serious genetic disorders, rather than techniques which could only minimise the potential for transmission. This view might mean that any woman at risk of passing on a mitochondrial DNA disorder might be a potential user of a cell reconstructive technology. We have not calculated whether permitting the option of cell reconstructive technologies to avoid mitochondrial disorders would create an overall cost saving to the publicly-funded health system.

4.49 In theory, the germline effect of the techniques make it more likely that subsequent generations in affected families could be born free from a high level of mutated mitochondria. This may be seen by currently affected families as a positive additional benefit to the procedure. Mrs Antonia Shaw responded to our call for evidence in light of her personal experience of living with a mitochondrial disorder. She wrote: "I am 58, live alone, have three adult children, spend most of my time in a wheelchair, use a ventilator at night, with the prospect of even more deterioration to look forward to in my health, but the knowledge that my children are affected, my daughter especially, leaves me with a feeling of complete desolation. They have my life to look forward to. [...] It is too late, I have passed on my condition. If there had been a method of prevention I would have sought it out and used it."[129]

4.50 Another respondent to the call for evidence, Lauren Griffiths, wrote: "I am writing in support of the research to prevent passing mitochondrial disease to the next generation. I am twenty one and was diagnosed with MERRF disease in 2002. I want to have children in the future but worry about the percentage of the mutation I would pass on. My affected family members have mutation loads of around 70% and suffer from a variety of devastating symptoms which affect their everyday life and independence. [...] It is every female's right to have children. There must be many women faced with the same dilemma as myself, whether to have children or not. If an end to mitochondrial disease for the future is a possibility then research into this should not be prevented. Women of child bearing age with these diseases are not asking for designer babies just children who will be able to grow up without devastating mitochondrial disease. The possibility of stopping the disease for the next generation, if the research was allowed to go ahead would be phenomenal. The end of mitochondrial diseases and the suffering it causes is a must for future children."[130]

4.51 The Muscular Dystrophy Campaign wrote that: "In the absence of a cure or treatment for these conditions, this technology currently has the amazing potential to transform lives by breaking the chain of inheritance within families:"[131] Although we may debate what the consideration of the interests of future people implies, techniques (in theory including PNT and MST) which could allow children to be born without the prospect of developing mitochondrial disorders, and allow female children not to transmit such disorders, may be particularly valued by some affected families because of their trans-generational impact.

4.52 It is likely that only relatively small numbers of people will seek to use cell reconstruction techniques should they become an acceptably safe and effective option in future. Given the potential seriousness of mitochondrial DNA disorders, it is reasonable that society should permit

[128] Kass L (2003) Ageless Bodies, Happy Souls *New Atlantis*, Spring Edition, p. 19. See also Lewens, T (in press) 'Human Nature: The Very Idea' *Philosophy and Technology*: published online, doi 10.1007/s13347-012-0063-x.
[129] Mrs Antonia Shaw responding to the Working Group's call for evidence, paragraphs 1 and 3.
[130] Ms Lauren Griffiths responding to the Working Group's call for evidence, paragraphs 1, 2, 5 and 6.
[131] BioNews (13 February 2012) Why we should back a law change to allow mitochondrial transfer into the clinic, available at: http://www.bionews.org.uk/page_124860.asp.

women seeking to avoid the transmission of mutated mitochondria to access such treatment. In publicly-funded health systems this seems a reasonable service to offer and one which is unlikely to disrupt the social order.

PNT and MST compared with other germline techniques: differences

4.53 Cell reconstruction techniques such as pronuclear transfer and maternal spindle transfer, as we have previously mentioned, have some implications that are different from those of other germline therapies.

4.54 As part of our call for evidence, respondents could consider the ethical distinctions between the prospect of germline therapies that would seek to:

- **transfer unaltered pronuclei** between embryos (as in pronuclear transfer)
- **transfer the unaltered nucleus** of a cell between embryos (as in nuclear transfer techniques)
- **seek to alter or modify** the nuclear DNA of an embryo (as in germline techniques that would act on the nuclear genes)

4.55 Various respondents expressed views amounting to a position that cell reconstruction therapies such as PNT and MST would involve distinctive ethical considerations because (as far as we know) they would act solely on mtDNA. These included, but were not limited to, the ethical consideration of issues of the personal identity of the resulting people, and the health risks inherent in proposed therapies. For example, the Progress Educational Trust responded to the Call for Evidence to state that: “mtDNA can … be said to be both genetically and epigenetically tangential to a person's ipseity. One reason why it is sometimes wrongly assumed that mtDNA is bound up with a person's ipseity, is because of a more general misapprehension that DNA per se is inseparable from identity. This notion has been promulgated widely in recent years, with the forensic use of variation to identify individuals among populations, and with public dissemination of the results of the Human Genome Project. But despite the popularity of this notion, it is far from being a generally applicable truth, and mtDNA is one of the starkest examples of an instance where it does not apply. […] … mitochondrial exchange can be characterised accurately as a form of human germline genetic modification, albeit a form of modification where DNA molecules are left completely intact (thereby avoiding risks posed by intervening in the gene sequence within the molecule). Because the provenance of properly functioning mtDNA is irrelevant to an individual's identity, altering mtDNA's provenance in a way that endures across generations is not ethically problematic […] … the most significant risks associated with human germline genetic modification do not apply in this instance….” [132]

4.56 Many respondents to the call for evidence mentioned the fact that the mitochondria only contribute a small proportion of genes to the embryo, in comparison to those in the nucleus. The Working Group considered that it might be possible to construct an argument that the proportion of genes affected by a proposed treatment is of ethical significance. On this view, interventions with an effect on a larger number of genes, which might theoretically affect a greater range of functions, would therefore be of greater ethical concern. However, the Group concluded that this position would be limited, if we note that important personal characteristics can be conveyed by only a small number of genes. For example, the Y chromosome contains only 86 genes, encoding 23 proteins, but being male is usually considered an important personal characteristic. If a treatment were ever proposed which would make interventions on the Y chromosome, this prospect would raise significant ethical questions, although only a small number of genes would be involved. Accordingly, the Working Group has tended to consider that the ethical concern lies not in the number or proportion of genes that would be affected by a treatment, but in the function of the genes that are acted upon. For example, many nuclear genes fulfil either a comparable, or identical function to mitochondrial genes.

[132] The Progress Educational Trust responding to the Working Group’s call for evidence.

4.57 If this is accepted, then it becomes difficult to draw meaningful ethical distinctions between therapies for serious conditions that would act on either the nuclear or mitochondrial genes. As mitochondrial disorders demonstrate clearly, defects in either genome can be the cause of wide-ranging and severe physical and mental symptoms. Patients in both groups would be likely to benefit if effective treatments or ways to safely prevent the transmission of inherited disorders became available to them. An effective treatment targeting either causative genome would be likely to have wide-ranging effects on many important functions. Dr Jackie Leach Scully, Professor of Social Ethics and Bioethics at Newcastle University, presented to a fact-finding session of the Working Group and acknowledged the difficulty of drawing distinctions between prospective treatments for mitochondrial disorders which would act on either the nuclear and mitochondrial genomes – if we assume that at some point in the future, potential methods may be proposed for preventing nuclear genes from transmitting mitochondrial disorders. Dr Scully noted: "It has been argued that mitochondrial modification is the thin end of the wedge towards heritable manipulation – and I think that may well be true. While it is theoretically possible to place blocks against it, for example by stipulating that only mitochondrial but not nuclear genes can be changed, in practice it is going to be hard when faced with real patients to explain that because the cause of their condition lies on 'the wrong kind of DNA', you can't intervene. So almost inevitably I think that there will be pressure to move towards other forms of genetic manipulation, especially if/when a particular case is taken up by the media. There is precedent for this in the 'saviour siblings' arena."[133]

4.58 The call for evidence produced arguments in support of future prospects for germline therapies such as nuclear transfer, which would transfer an unaltered fully-developed cell nucleus between embryos. The British Medical Association stated that they supported the use of nuclear transfer techniques to avoid severe mitochondrial diseases: "For some people.. the merging of the [pronuclear] DNA from the parents to create an embryo with a unique genetic identity is morally significant. Those holding this view are likely to find [pronuclear transfer] morally preferable [to nuclear transfer] because of the higher moral status afforded to the embryo once this stage of development has been reached. Given, however, that the law permits research up to 14 days after fertilisation where it is 'necessary and desirable', and the BMA supports this position, the BMA does not consider this to be a relevant distinction in terms of developing policy for mitochondrial transfer. It has also been suggested that it is morally significant that [prospective treatments involving nuclear transfer] use the same technology as would be used to clone an embryo, but the BMA has always argued that it is the intention to create genetically identical individuals that is problematic about human cloning, rather than the technology itself. This is not cloning and should not be considered as such."[134]

4.59 By contrast, the response to the call for evidence from the Anscombe Bioethics Centre stated that: "The pronuclear stage of embryonic development is not ethically (or, indeed, legally) different from the two cell stage. PNT … is a form of reproductive cloning – in this case, from an embryo. […] PNT should be considered unethical because, in addition to the problems of germline genetic engineering which it shares with MST, PNT is a particularly destructive form of human cloning." [135] Comment on Reproductive Ethics (CORE) also stated that: "Pronuclear transfer involving a developing embryo is a cloning procedure."[136] This observation is in principle accurate in noting that elements of the pronuclear transfer process (i.e. the transfer of genetic material) are the same as elements of the process used in nuclear transfer or even somatic cell nuclear transfer. However, the Working Group noted that it would only be appropriate to label every technique that used genetic transfer a 'cloning' procedure, if a similarity in some elements of a procedure was the only relevant factor used to delineate that

[133] Oral presentation given by Dr Jackie Leach Scully, Professor of Social Ethics and Bioethics at Newcastle University, to a fact-finding meeting of the Working Group in London, 17 February 2012.
[134] BMA response to the Working Group's call for evidence.
[135] Anscombe Bioethics Centre, responding to the Working Group's call for evidence, at paragraph 2.1.
[136] Comment on Reproductive Ethics (CORE), responding to the Working Group's call for evidence, at paragraph 3.

category. Other ethically relevant factors that might create sharp distinctions between different techniques of genetic transfer include the proposed treatment's purpose, its outcome and whether it brings into being 'copies' of another individual, and the nature of the genetic material that it would involve or affect.

4.60 Taking into account these other factors, the Working Group has not found it appropriate to describe pronuclear transfer as a cloning procedure. The Group noted important differences between for example, human reproductive somatic cell nuclear transfer and cell reconstruction techniques. In particular, it was noted that PNT does not transfer a fully-formed nucleus, nor 'clone' a pre-existing 'original' individual or entity. Instead PNT constructs a new embryo which incorporates pronuclei formed by sexual reproduction in the usual way, uniquely reflecting its maternal and paternal genetic contributors. Complex technical differences are also apparent between the methods of performing cell reconstruction and somatic cell nuclear transfer techniques. In reproductive SCNT, the nucleus taken from a somatic cell (for example, a sheep's mammary gland in the case of Dolly the sheep) must be 'reprogrammed' to behave as if it were in an embryonic state. No such manipulation of the pronuclei (nor any other part of the reconstructed embryo) is required in PNT.

PNT and MST compared with other germline techniques: similarities

4.61 The Working Group did not have the remit to explore in detail the ethical issues raised by different types of germline therapies which would act on the nucleus, including the various forms of nuclear transfer or 'cloning'. However, the Group noted that therapies which would act on either the nuclear or mitochondrial genomes raise common ethical questions, for instance because their effects are not confined to the individual that would develop from the embryo that is the immediate subject of the therapy, but would be inherited by future generations that may descend from that person.

4.62 It is a question for further debate as to whether techniques which would make therapeutic germline changes via mitochondrial genes should be regarded as substantially ethically different from techniques which would make therapeutic germline changes via the nuclear genes, if concerns about safety and efficacy could be answered in both instances.

4.63 That said, some may argue that PNT and MST should be objected to because if they were permitted as treatments this would create ethical or regulatory 'slippery slope', in which nothing would stand in the way of genuinely troubling germline alterations which would act upon nuclear genes, if these were to be proposed in future.

4.64 For example, Professor Brenda Almond made the following submission to the Working Group's call for evidence: "The UK takes pride in pioneering scientific research [...] clearly there are potential profits to be made from biotechnological innovation and its medical deployment. But pioneering the clinical application of research that has so far been regarded as an absolute ethical no-go-area- research, that is, that clinicians in the Western democracies have so far regarded as impermissible – should prompt careful thought. There are two aspects to the uniqueness of the proposed procedure: i) that it involves reconstruction (genetic engineering) rather than selection, and ii) that the germline is affected – any effect of the modification will be passed on to future generations (it is anticipated that the effects will be benevolent but prediction is risky). For good reason, then, this is a line that has so far been regarded as not to be crossed. To cross it in this one case is to open a Pandora's box hitherto kept firmly sealed – and it is difficult not to believe that once that box is opened, germline therapy will be regarded as an acceptable option in other cases as well. In other words, we might expect that, once the ethical arguments used to restrain moves toward designer babies have been swept aside in this

one instance, momentum would grow to legalise interference with the nucleus of the human egg as well as with the mitochondria. The much-debated 'designer baby' would become a reality."[137]

4.65 The Working Group concedes that many ethical objections to germline interventions are of a generic form which applies equally well (or not at all) to both mitochondrial and nuclear transfer, or nuclear modifications. That said, in our view the clear material difference between mitochondrial and nuclear genes means that in practice the adoption of PNT or MST would not necessitate the further adoption of either nuclear transfer or nuclear modification technologies as treatments, if these emerged in future. The fact that there is a distinct material boundary between mitochondrial and nuclear genes allows regulators to establish an equally clear legal distinction between modifications to the different genomes, thereby forming a practical barrier to the threat of 'slippery slope' arguments. Such a barrier may well be prudent, given uncertainties regarding the risks of further germline modification. Moreover, important concerns relating to the costs and benefits of such interventions which would act upon the nuclear genes could quite conceivably lead to a different verdict regarding their ethical permissibility.

Experimental treatments and risk

4.66 In the immediate future, the PNT and MST techniques are likely to be the subject of further studies including human embryo and animal research stages before being considered by the Secretary of State for treatment in the UK.[138] However, in common with other medical innovations, even if they are approved as treatments in due course, in their early years of use they might still be considered as experimental. In respect of their germline effects, this status would remain across several generations.

4.67 In general, assisted reproductive technologies are likely to result in pregnancies and the birth of children and so do not permit a clinical trial in the usual sense. They cannot be gradually phased into use. Any side effects may not be reversible or treatable. New reproductive treatments can be withdrawn from licence if problems are later observed (as the FDA sought to do with the CT technique in the US), but by that stage it is possible that individuals will have already been adversely affected by them. Ultimately, parents will decide whether to create children who must live with any problems generated by the procedure, where the law and resources permit them to do so. If treatments are not permitted in their own jurisdiction but available elsewhere, experience from other forms of assisted reproduction suggests that some prospective parents will travel to access these, if they have the resources to do so. Travelling to access treatments may create issues of a lack of equality of access, legal problems for the status of the resulting child, and difficulties regarding medical follow-up of the child.

4.68 New assisted reproduction treatments tend initially to be offered to very small numbers of people with the aim of close follow up, with parents deciding whether to participate in follow up, and for how long. Should cell reconstruction treatments be licensed in the UK or offered elsewhere in the world, a challenge for providers will be to facilitate access for families who wish to try them within an ethically robust setting that acknowledges known risks and updates this information by gathering new evidence about the children born. The history of assisted reproduction treatments does not show that this has been easily achieved. However, if novel techniques such as these are to be introduced, they must be accompanied by appropriate follow-up of the families and offered within a research setting.

4.69 People working in assisted reproduction often note that treatments they offer routinely, such as IVF, ICSI and PGD could not have been moved directly into treatment use today in the same

[137] Professor Brenda Almond, Emeritus Professor of Moral and Social Philosophy at the University of Hull, responding to the Working Group's call for evidence.
[138] Human Fertilisation and Embryology Authority (2012) *Review of scientific methods to avoid mitochondrial disease 2011*, available at: http://www.hfea.gov.uk/6372.html.

way as has happened historically. IVF was moved into treatment in the 1970s after research on the safety of animal IVF had been produced, but in the 1990s, ICSI was introduced with no previous successful animal studies. Human ICSI has since led the way to achieving the technique in animals. While some contemporary methods for collecting safety data were not available in the past, it can be argued that today, we expect a higher standard of information to be available in order to safeguard the first generation of people born from ARTs (assisted reproductive technologies). This could particularly apply to PNT and MST because they create germline effects. Existing treatments may offer some information about the likely safety of PNT and MST, but an adequate body of specific research will be required to allow prospective patients to balance their wish for genetic connectedness against a level of estimated risk that is acceptable to them.

4.70 A respondent to the call for evidence, Professor Mary Herbert, a researcher working on PNT at the Newcastle Centre for Life, commented that: "A number of now established procedures in the assisted conception field have been introduced without extensive experimental testing. In this sense the approach to the possible introduction of PNT/MST represents a welcome new departure. The expert review panel convened by the HFEA on behalf of the Secretary of State has outlined a programme of experiments to be conducted before the techniques can be considered for use in clinical treatment. Significant funding has been obtained to pursue the experiments outlined by the expert review panel. The research, which is currently underway, will inform the regulatory process. In the event of the PNT/MST being translated to clinical treatment, the research evidence will be important in informing patient choice. This point has ethical relevance as the decision making process for patients is likely to be easier if we can provide a reasonable estimate of the probability of producing a viable pregnancy in which the fetus carries low levels of mtDNA mutation. While the findings of ongoing research into PNT/MST will help to inform patients considering these treatments, obviously it will not be possible to gather information on live births until the techniques are offered in clinical treatment. Thus, an element of risk will remain. This is analogous to the situation for other techniques in assisted conception and indeed in many other areas of medical practice. In this respect, there is therefore no new ethical dilemma."[139]

4.71 It is not in our remit to propose which specific data and in what quantity should be gathered before PNT or MST could be considered for treatment use. But we welcome the scientific discussion on this and note that researchers have identified some priorities for further research. For example, further studies using human embryos and research with animals will be important to disclose any potential for the manipulation of embryos and gametes to cause chromosomal or epigenetic problems.[140]

4.72 Also, while in conventional human sexual reproduction, men and women carrying different types of (healthy) mitochondria have had children together to no ill-effect, little is yet known about the interaction of the mother's and donor's mitochondria when artificially placed together in the same egg or embryo.[141] Cell reconstruction techniques have yet to be developed to a stage where there is no carry-over of mitochondria from the maternal source into the donor egg or embryo. This might prove never to be possible, so more information will need to be gathered about this. Interaction between the nuclear and mitochondrial DNA is essential for normal embryo development. Therefore further research involving reconstructed embryos will be important in establishing to what extent nuclear and mitochondrial DNA from two different women can interact normally or effectively when placed together via cell reconstruction.

4.73 Another potential risk presented by PNT and MST as they are currently performed, is that they use agents not normally used in reproductive embryology. Pronuclear transfer uses Nocodazole

[139] Professor Mary Herbert, Newcastle University, responding to the Working Group's call for evidence, at paragraph 3.1.
[140] Craven L, Tuppen HA, Greggains GD *et al.* (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease *Nature* **465**: 82-5.
[141] Spikings EC, Alderson J, and John JCS (2006) Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer *Human Reproduction Update* **12**: 401-15.

(to restabilise the cytoskeleton after penetration of the membrane of the egg with the micropipette used to transfer the two pronuclei), and maternal spindle transfer uses inactivated Sendai virus (to facilitate fusion of the membrane enclosed chromosomes after spindle transfer).[142] Both agents have been used for decades in micromanipulating research embryos in the lab, but there are no safety data for human reproductive use. However, since the effects of these agents are dose dependent and known to be reversible, it is possible that they can be 'washed out' of a reconstructed cell and may not cause problems.

4.74 Further research using human eggs may also be needed to establish how mitochondria behave and are distributed in the individual cells of early embryos, including at the blastocyst stage (which is when PGD would be done) and as the embryonic cells differentiate during development into stem cells. This will also establish whether individual cells have predictable and uniform mitochondrial proportions at these early embryonic stages (and to what extent they can offer clear information when biopsied in PGD to help indicate any genetic risk to the future child).

4.75 A different type of risk relates to children that might descend from a person born after the initial cell reconstruction treatment. We don't as yet know a great deal about how effectively a cell reconstruction procedure might prevent mitochondrial disorders from occurring in future descendants. Benefiting future generations that may descend from the child born via cell reconstruction is not the primary reason why these techniques would be performed. However, it has been noted that there may be a theoretical risk that, over time, the subsequent generations born from people who were themselves born from the MST or PNT techniques would no longer have a substantially lowered risk of inheriting a high level of mutated mitochondria. If this phenomenon eventuated, it would have been caused by the carry-over of the original (mutated) maternal mitochondria, which might be unavoidably transferred into the reconstructed egg/embryo.

4.76 Like other techniques in assisted conception such as ICSI, individual technical skill and familiarity of the operator with the technique may influence its outcome: in this case how much carry-over of (possibly mutated) mitochondria is deposited in the donated egg. Theoretically, if sufficient carryover of mutated mitochondria occurred at the time of the cell reconstruction, over a few generations descended from the person born from the reconstructed embryo, a small carried-over population of mutated mitochondria could be 'amplified up' through the mitochondrial bottleneck as eggs are developed, to reach levels high enough to create the symptoms of mitochondrial disorders in future children. In a scenario where cell reconstruction treatments might be offered by a number of different practitioners, the range of carry-over might need to be monitored in the same way that damage to eggs at ICSI is audited. Some researchers suspect that the influence of the nucleus on the mitochondria may give a replicative advantage to particular types of mitochondria.[143] Further research could establish whether any carried-over (mutated) mitochondria from the mother may be able to preferentially replicate and populate the reconstructed embryo over the healthy mitochondrial population in the donor's egg.

4.77 Concerns have been raised as to whether it is reasonable to use experimental techniques in avoiding mitochondrial disorders at all, given that alternatives are available for parenting healthy children, and for preventing the birth of an affected child. However this objection can be extended to most forms of assisted reproduction and does not specifically apply to cell reconstruction techniques so the Working Group did not explore it in depth. The risks of the alternatives to PNT and MST were discussed as part of the Working Group's consideration of

[142] The use of Sendai virus rather than electrofusion for this purpose is described in maternal spindle transfer in primates: Tachibana M, Sparman M, Sritanaudomchai H *et al.* (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells *Nature* **461**: 367-72.

[143] Moraes CT, Kenyon L, and Hao H (1999) Mechanisms of human mitochondrial DNA maintenance: the determining role of primary sequence and length over function *Molecular Biology of the Cell* **10**: 3345-56.

routes to parenthood for women affected by mitochondrial DNA mutations. For those unwilling or ineligible to use PGD to minimise the risks of transmission, adoption would allow women with a high proportion of mutated mitochondria to bring up children. Egg donation could offer them the additional possibility of gestational motherhood. Neither egg donation nor adoption pose new safety risks in the way that novel treatments may do. However, neither egg donation nor adoption is risk-free in terms of psycho-social effects for parents and children, and in the case of egg donation, the recipient and donor incur established health risks by participating in IVF treatment. Some parents might decide to conceive naturally knowing that they risk having an affected child, such is their interest in using their own gametes to create a pregnancy.

4.78 Like any other prospective parent, some people seeking to have unaffected children may hold very strong feelings about their preferred route to family formation in addition to their goal of seeking to have healthy children. For a range of reasons, the existing options to avoid the transmission of inherited mitochondrial DNA mutations may not be ones they want to take up, even if they would be eligible to do so.

4.79 The Working Group is aware that most reproductive technologies have been developed in order to allow people to have a child with whom they share a genetic or biological connection, and/or to enable women to carry a pregnancy. The desire to have a genetic connection to children, and for some women the desire to experience pregnancy, is recognised as a widespread and often very deep desire. This drive is often described as being natural or even instinctive, whilst also being influenced by contemporary cultural and social norms. However, the drive felt by many men and women to have a genetic connection to their children is largely accepted by society and in seeking to make this possible, new reproductive techniques have been created, often entailing some level of health risk to the mother and/or the resulting child. It was also noted, however, that many people consider that a genetic connection (or the lack of it) is unimportant in their parenting of their children – and that other people do not seek to become parents at all.

4.80 Some factors of risk that would need to be considered by clinicians providing PNT and MST are common to all fertility treatments offered under the HFE Act. The Act requires licensed centres offering fertility treatments to ‘consider the welfare’ of any future child that may be born. If the potential mother is affected by a serious mitochondrial disorder, she may have a limited ability to care for a child and may have a reduced life expectancy. While this is a potentially relevant consideration to all forms of child bearing (naturally conceived or otherwise) if some form of assisted conception is used, the treatment centre is legally obliged to consider what impact the mother’s health may have on the welfare of any future child that is born. In extreme cases clinicians might feel that offering fertility treatment (including PNT or MST) might not be consistent with protecting the welfare of any future child that is born, so treatment may be refused.

4.81 A discussion paper written for the Human Genetics Commission has sought to identify the key factors that would need to be weighed up before cell reconstruction techniques were offered. It considered only the risks to the first generation to be born from techniques to prevent transmission of inherited mitochondrial disorders. The paper posits that:

“There are four theoretically possible outcomes of mitochondrial transfer which, collectively, would need to be weighed against the available alternatives (including childlessness, gamete donation, PND and PGD and having an affected child) before any treatment could be initiated. These are:

1) The pregnancy may spontaneously abort. (The treatment may or may not have an effect on the likelihood of this outcome.)

2) The fetus may be affected more severely than it would be by the mitochondrial disorder due to iatrogenic effects. If this is detected through PND the pregnant woman may elect to terminate or continue the pregnancy and have an affected child. If it is not detected through PND and the pregnancy continues to term, an affected child will be born.

3) The fetus may be affected less severely than it would otherwise be by the mitochondrial disorder owing to partial success of the treatment. If this is detected through PND the pregnant woman may elect to terminate or continue the pregnancy and have an affected child. If it is not detected through PND and the pregnancy continues to term, an affected child will be born.

4) The treatment may succeed and the pregnancy will continue to term, with the resulting child being free from the symptoms of mitochondrial disease."[144]

4.82 We would add further outcomes for consideration, namely that:

- Given a possible lack of certainty about the power to predict the risk of mitochondrial disorders using PGD, a clear prognosis for the future child after the use of cell reconstruction therapies might not be discernable via the use of PGD. The prospective mother will need to decide whether or not to proceed with transferring an embryo to her body.

- Alternatively rather than use PGD after PNT or MST, the couple may wish to avail themselves of PND if a pregnancy develops, bearing in mind the possibility of uncertainty in prediction at this stage if there are some mutated mitochondria still present, and the small risks of miscarriage entailed by invasive PND sampling techniques.

- The pregnancy may continue to term after PNT or MST, and the child is born healthy or only slightly affected due to a minimal carryover of mutated mitochondria. However, because of the hard-to-predict process of mitochondrial inheritance, if there was any inadvertent carryover of mutated mitochondria as part of the transfer process, after a few generations, the children descended from females created by PNT or MST could possibly be born with as serious, or even more serious mitochondrial mutations than their mothers. However, this is not a concern that policymakers need factor in to their decision as to whether the treatments should be permitted, as their chief ethical concern should be the child to be born as a result of the treatment. Achieving a healthy baby may be a worthwhile use of the technology even if that health benefit does not persist for its descendants. This is more a matter to be discussed in specialist counselling, as some parents have cited the hope of eradication of mitochondrial DNA disorders as a strong possible benefit of undergoing the procedure, in a similar way to parents who use PGD to avoid dominantly inherited nuclear DNA mutations, such as Huntington's disease. As this trans-generational assurance cannot yet be given, some parents may prefer to take up an alternative to cell reconstruction therapies.

4.83 All of the above outcomes would need to be considered by policymakers before proposing regulation. If cell reconstruction treatments are permitted in the clinical setting, these outcomes should also be discussed with patients (where they are relevant based on the latest available research information), in order to give them the opportunity to determine a personally acceptable level of treatment risk.[145]

4.84 The same information should also be discussed with any potential donors of mitochondria in order to fully inform their decision to donate. The current legal requirements for reproductive gamete donation as interpreted by the HFEA, include that donors be given enough information

[144] HGC (2010) *Paper HGC10/P07: Discussion of ethical issues in human reproduction using material containing DNA from more than two sources – Annex A*, available from HGC. See also for further information: HGC (2010) *Paper HGC10/P07: Ethical issues in human reproduction using material containing DNA from more than two sources*, available at: http://www.hgc.gov.uk/Client/document.asp?DocId=266&CAtegoryId=9.

[145] It may not be the case that providing treatments will decrease concern about risk. For example, women born after PNT or MST may have concerns about the potential risks of passing on unforeseen problems to their own children and to future generations brought about by the PNT or MST procedures. It should not be assumed that because PNT and MST could stop women from passing on mutated mitochondria, an overall improvement in their reproductive confidence would be the result.

to enable them to understand the nature, purpose and implications of their donation.[146] This would include allowing donors to consent to procedures to which they understand the outcome may be uncertain.

4.85 Finally, the Working Group discussed the risks that would be incurred if regulation to permit PNT and MST to be offered were not introduced. Most obviously, where potential parents choose not to use available alternative approaches to avoid these disorders (or are not in a position to do so) the risks would include that more children are likely to be born with mitochondrial DNA disorders, potentially resulting in very serious illness and shortening of their lifespan. A clearly-defined group of patients would continue to have no option of having a healthy child with whom they share a genetic link, limiting the exercise of their reproductive autonomy, which could have adverse emotional and other consequences for themselves and their families. In some cases, women would be exposed to the unnecessary health risks of termination(s) of pregnancy in the second and third trimesters in order to avoid mitochondrial DNA disorders predicted after PND, which might have been avoided had PNT and MST been available to them.

Social relationships formed by donation and assisted reproduction

4.86 Social significance tends to be ascribed to the donation of human tissue according to its context. Donors' and recipients' individual experiences of forming social relationships brought about by the donation of organs or tissue (or of a desire to form them) vary across and within different treatments. This is seen in the differing expectations around the subsequent social roles of, for example, blood, egg, sperm, or live kidney donors in relation to recipients and their families.[147]

4.87 There is no evidence as to how a donor giving an egg intending her mitochondria to be used (rather than her nuclear DNA) might regard the social significance of her donation. It is possible that mitochondrial donors may have different views of the social meaning of this donation as compared to donating their eggs for reproduction or research. However, there is no research on whether being treated in regulation like an egg donor for reproduction (or for research) would be acceptable to mitochondrial donors.

4.88 Similarly, there is no evidence from people born after the use of cell reconstruction techniques regarding their perspectives of any social relationship to their mitochondrial donor implied by the donation. This issue has been particularly discussed because people born from PNT or MST would be amongst the first to be born with a genetic connection to three people, albeit with a very much smaller genetic contribution coming from the donor. The resulting people would inherit nDNA (circa 20,000 – 30,000 genes) from their parents' sperm and egg, and healthy mitochondrial mtDNA (37 genes) from the donor of the enucleated egg or embryo. It's also possible that they may receive a very small amount of mitochondria from their mother's egg, dependent on the level of carry-over involved in the technique used.

4.89 The first-ever children to be born with a genetic connection to three people were born via the cytoplasmic transfer (CT) technique in the 1990s. They have a nuclear genetic connection to a man and a woman (and a mitochondrial connection to the same woman), plus an additional mitochondrial genetic connection to a second woman provided by an injection of her cytoplasm. As far as the Working Group is aware, no work has been published on the perception of people born by CT of any social relationship to the mitochondrial donor, nor vice versa with cytoplasmic donors.

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[146] Human Fertilisation and Embryology Authority (2009) Code of practice: consent to treatment, storage, donation, training and disclosure of information - interpretation of mandatory requirements: 5B, available at: http://www.hfea.gov.uk/336.html#mandatoryAct.

[147] See, for example, the Nuffield Council's recent report on Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: http://www.nuffieldbioethics.org/sites/default/files/Donation_full_report.pdf.

4.90 Whilst it is difficult to predict what a resulting person's perception may be of any social relationship brought about by a genetic connection to the mitochondrial donor through cell reconstruction techniques intended to prevent mitochondrial DNA disorders, this seems likely to depend on various factors. These might depend on how the resulting person (or his or her social circle) feels that the balance of social relationships and genetic connections inform personal identity. As with all of our relationships, many aspects of this perception will depend on each person's unique situation.

4.91 Some argue that feelings of ambiguity about the genetic and social roles of the three adults who have contributed to their genetic makeup may compromise the resulting child's wellbeing or sense of identity. For some, this is of sufficient concern to question whether such research techniques should be offered as treatments. Ethicist Professor Brenda Almond responded to the call for evidence to argue that: "People are increasingly concerned to understand their own complex genetic inheritance and to have access to the world of their genetic relations – a biological family that includes grandparents, aunts, uncles and cousins, as well as forebears and descendants. This fabric of connections has until now formed the webbing underpinning most known cultures and societies. But children born by this procedure would need to be given information about their three genetic sources, and this is likely to be confusing for their sense of personal identity. [...] people are increasingly concerned to locate themselves in their biological network, which has until now provided the individual's deepest conception of their identity and in many cases offered them the social space within which to find their earliest sense of self. This is why comparison with organ or tissue transplantation and with donation of other bodily material is completely inappropriate. [...] ... the reservations of those who fear the commodification and trivialising of human life are understandable, and it might well be that the balance should fall on the side of caution – that we should conclude, that is, that the boundaries of reproductive medicine are rightly narrower than the boundaries that govern scientific research."[148]

4.92 Josephine Johnston, a US bioethicist and lawyer (writing regarding children born via CT), by contrast does not see children born with genetic connection to three people as a worrying departure, given the existing variety of parenting arrangements in families: "…what might be wrong with creating a child using genetic material from three or more people, or from only two men, or only two women? In a world already familiar with the distinction between 'genetic' parents and 'social' parents, with step-dads, and with families that have two mommies, why does every child have a right to have been created from the 'union' of one man and one woman? Is such a right really necessary to protect the welfare of children? [It is]... wrong to think that having a different kind of genetic origin necessarily causes harm. Unless we tell children that, due to how they were created, they are flawed or incomplete persons, what will really matter is that these children are loved and cared for by a nurturing family. They have a right to be fed, clothed, treated with dignity, and protected from harm – they even, I think, have a right to be (or a strong interest in being) told the truth about their genetic origins. But they don't have a right to have been created from the genetic material of only one man and one woman. To insist otherwise is to pull us back to a time when one's genetic origins determined one's worth." [149]

4.93 In respect of mitochondrial DNA donation, UK bioethicist Dr Jackie Leach Scully submitted to us that the impact of being born with three genetic contributors on the resulting child's sense of self is likely to be influenced by the attitudes of other people towards the child's genetic background: "Having three parents is not unusual; being born as a result of 'generative input' from 3 parents these days is unusual but not unprecedented; but being genetically related to three people is novel. In my opinion this aspect is the most likely to affect the child's sense of self, not through any influence of the DNA but though intersubjective personal identity and the creation of

[148] Professor Brenda Almond, Emeritus Professor of Moral and Social Philosophy at the University of Hull, responding to the Working Group's call for evidence.
[149] Johnston J (2007) Tied up in nots over genetic parentage *Hastings Center Report* **37**: 28-31.

unusual family lineages and social relationships. Here the question is whether families and societies have the capacity to accommodate to this as a 'new kind of normal', and if not, to what extent that lack of accommodation will be problematic. This is not to say that being genetically related to three people is of itself ethically troubling, and this need not inevitably be socially problematic. Precedents show that families and societies can be enormously flexible in what they take to be 'normal', and can adapt to novel situations with surprising ease. The issue here is more about identifying what factors and features make this more likely and make problematic responses less likely."[150]

4.94 In mitochondrial donation, it is difficult to predict the social role that the donor may play in the life of the resulting child as the social role of the egg donor is likely to differ widely between recipient families. In egg donation for reproduction (including in 'genetic' or 'full' surrogacy where a woman also provides her egg to create the child) these relationships vary depending on the circumstances of the donation and whether it has been disclosed to the child.[151] Having said this, recent decades have seen a rise in emphasis on the view that greater information should be passed to donor conceived people about the fact that a donor was involved in their conception. In 2005, new regulations assented to by Parliament meant that UK egg and sperm donors for reproduction through licensed clinics became the only tissue or organ donors not able to offer their donation anonymously.[152] Parents have no corresponding legal duty to inform their children that a donor was used in their conception, but donor-conceived people aged 18 and above can approach the HFEA for identifying and other information about their donor. There are also systems available to facilitate contact with genetic half-siblings from the same donor.[153]

4.95 In 2012, the HFEA launched a national strategy to raise awareness, improve the care of donors and to encourage increased numbers of reproductive gamete donors to come forward.[154] Interestingly, as part of the HFEA's message to encourage donation they referenced other kinds of tissue and organ donation usually provided on an anonymous basis. These introduce donated genes to the recipient, but not in a way that can be passed on to the recipient's descendants. The BBC reported that: "The UK fertility regulator is seeking to reduce the taboo around egg and sperm donation. The Human Fertilisation and Embryology Authority (HFEA) says people should feel the same about it as they do about altruistic, or living, organ donation." HFEA Chair Lisa Jardine was quoted in the *Daily Telegraph* as saying that she wanted egg donation to become "as obvious as blood donation".[155]

4.96 In fact there may be some opportunities for possible contact between donors and recipients of other organs and tissue, but this seems to vary according to local policy. According to some policies, donors of live organs and tissue may be given information about the outcome of the donation, or contacted by letter from recipients if they give consent to this. This contact is conducted via an intermediary organisation. Some policies allow consenting donors and recipients to meet, but others forbid it. Families of deceased organ donors may also be sent

[150] Oral presentation given by Dr Jackie Leach Scully, Professor of Social Ethics and Bioethics at Newcastle University, to a fact-finding meeting of the Working Group in London, 17 February 2012.

[151] *The Daily* Mail (28 May 2012) The Heartbeat star, his wife and the woman their children call 'egg mummy': couple treat fertility donor like a member of the family, available at: http://www.dailymail.co.uk/health/article-2150818/Heartbeat-star-Jason-Durr-wife-treat-fertility-donor-like-member-family.html; *The Guardian* (14 May 2011) Donor eggs: But will the baby feel like mine? available at: http://www.guardian.co.uk/lifeandstyle/2011/may/14/donor-eggs-pros-cons-conception; and *The Daily Mail* (28 April 2011) Ann doesn't want a baby... so why has she risked her health to give life to two children as an egg donor?, available at: http://www.dailymail.co.uk/femail/article-1381253/Ann-doesnt-want-baby--risked-health-life-children.html.

[152] The *Human* Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004, available at: http://*www*.legislation.gov.uk/uksi/2004/1511/contents/made.

[153] HFEA (2012) Donor Sibling Link (DSL): Contact your donor-conceived genetic siblings, available at: http://www.hfea.gov.uk/donor-sibling-link.html.

[154] Human Fertilisation and Embryology Authority (4 April 2012) *Fertility regulator launches strategy to boost egg and sperm* donation, available at: http://www.hfea.gov.uk/7142.html.

[155] The Telegraph (4 April 2012) *Sperm and egg donation 'should be like giving blood'*, available at: http://www.telegraph.co.uk/health/healthnews/9185916/Sperm-and-egg-donation-should-be-like-giving-blood.html#disqus_thread.

information about the outcome of the donation, or receive letters from recipients if they consent to this. However it is very rare that arrangements would be put in place to allow them to meet and some local policies explicitly forbid this. While the emphasis on altruism and the implied social solidarity seen in the HFEA's drawing together of different types of altruistic donation has much to commend it, some of those who represent donor conceived families have noted the differences between these kinds of donation with concern.[156]

4.97 It is not yet clear what the regulatory approach might be towards making information about mitochondrial donors accessible to the resulting people, in the event that cell reconstruction treatments were permitted to be offered in the UK. The Working Group discussed whether it might be important for mitochondrial donors in the UK to be mandatorily identifiable in the same way as reproductive gamete donors. This point was raised by some respondents to the call for evidence, including the BMA: "The child will be the child of the intended parents whose nuclear DNA is used to produce the embryo from which the child has developed. The donor of the mitochondrial DNA should not be considered in the same way as an egg donor since her contribution is to provide an energy source for the cells only. Although there is still much that is unknown about the role of mitochondrial DNA, the scientific consensus is that it does not have any influence on the characteristics of the child. The reason children born following donor conception require information about the donor is because the information relates to them as a person, and the donor's genes have contributed to that person's physical appearance and personal characteristics. The same does not apply to mitochondrial DNA."[157]

4.98 The responses to our call for evidence included some comments from patients noting that they would tell a child, born via cell reconstruction, about their genetic connection to the mitochondrial donor. Beth Wilkes wrote: "I am a carrier of an affected mitochondrial mutation, which I did not know about until my son of 8 weeks was diagnosed with Leigh's disease. He died 5 weeks later. [...] If I went down this route [pronuclear transfer] I would seek help from a friend. I wouldn't have any reservations in asking a friend because they wouldn't be giving me a baby with their characteristics or their genetic makeup, they would be giving me a baby with the energy to survive. Would I tell my child? Of course! I think it's something to be very proud of, and my child would grow up thinking they were a miracle of science. I would not use such words as "you have three parents" because that is ridiculous. I will simply tell them that someone special gave them the energy that makes them function. They would have no reason to want to meet with the donor, because there would be no genetic link. The only reason they would want to would be to say thank you. I would prefer not to travel overseas, but I would because I would do anything to have a healthy child. [...] So I am 100% in support of this procedure. Losing a child is the most devastating thing a parent can ever go through. You never get over it, but by having this procedure pass through law would enable so many devastated families move on in their life. It will never be the same, but it will help them move on without the apprehension of losing your child again."[158]

4.99 Melissa Rippon responded to the call for evidence, writing that: "Our son died 5 months ago from mitochondrial disease, Leighs disease. There is no family history. He was 2yr and 4 mths old. He had very little quality of life and was very ill and suffered greatly, as did the entire family. These last couple of years have been devastating beyond belief for all of us. We have one healthy daughter who is nearly 5. We would love more children to make our family complete but cannot take the risk this could happen again, so until our gene is found, we are pursuing donor egg options. We have travelled abroad to seek donor egg treatment. If this new treatment was available to us, we would definitely use it. We would 100% inform any child born of the techniques used, and feel strongly that the child would be grateful to have a genetic link to myself (mother) rather than no genetic link at all (with the donor eggs we are currently using). I

[156] See, for example, Montuschi O (2012) So what is this National Donation Strategy Group? *Oliviasview* [internet blog] available at: http://oliviasview.wordpress.com/2012/04/10/so-what-is-this-national-donation-strategy-group/
[157] BMA responding to the Working Group's call for evidence.
[158] Beth Wilkes responding to the Working Group's call for evidence.

believe the impact on the child would be minimal. It only takes me telling them the story of how our son died to make them realise why we would have pursued this technique to ensure another child didn't suffer this way. We would 100% travel abroad for this technique, we are already going to Spain for our donor eggs. I believe the donor would be just that – the donor. A kind and generous person that has given a wonderful gift to a mother who has been unlucky enough to have mitochondrial disease destroy her life and her family. The donor would be an amazing person to give such hope and chance to a broken family. I believe I would be the mother as I would have carried the child and given birth to it and raised it, and it would also have my genes. The donor would be the secret fairy godmother that enabled it to be a healthy child without a mitochondrial shadow hanging over them." [159]

4.100 Others said that they would not tell a child born via cell reconstruction about the mitochondrial donation. Andrea Williams wrote: "I feel it is a good thing to be able to have the chance to prevent passing on the Mitochondrial disease. I am a patient who suffers from Mitochondrial disease. My mother passed it down to my brother and I, and now I have passed it on to my seven year old daughter. We all are visually impaired and as we get into our 20s+ we suffer slow deterioration of sight, muscle weakness and in our late 20s+ problems with hearing too. When I was pregnant with my daughter there was not even a test to see if she was affected before she was born. I think it should be available to have the treatment where an egg donor is involved, especially as it is only the Mitochondrial cells that are being used from the egg donor and the child will still have all the characteristics of the parents. If I'd had the opportunity to have the chance to prevent my daughter from suffering from the disease I would have had the treatment. I would have no need to tell her about the treatment. It has been mentioned about the psychological effect it would have on your child if you told them about the third parent. I do not think it is necessary to tell the child as it is only the mitochondrial cells taken not the whole egg, and I feel there is a lot more to deal with mentally coping with the mitochondrial condition and feeling guilty passing the disease on to your child. Being the person in the middle generation of my family with the disease I have the psychological problems of seeing what problems I have to come, as my mother is blind deaf and unable to walk now and seeing what difficulties my daughter has lying ahead of her. In a generation the awful disease could be wiped out. This would be great for all those families suffering with Mitochondrial disease and save a lot of money for the NHS in the future."[160]

4.101 While the Working Group did not have the remit to look in depth at the growing body of literature around the experiences of people born from sperm and eggs donated for reproduction, the Group considered how such reported experiences might potentially inform the issue of whether mitochondrial donors should be required to be identifiable.

4.102 A key element complicating the assessment of the evidence around how donor conceived people in fare in general, is the fact that in the past only a minority of people were told that they were conceived with the use of donated gametes. Parents' reasons for disclosing the fact of gamete donation (or not doing so) may be complex and reflect many personal and cultural factors, including whether or not the donor can be identifiable to the child in future. Parents might disclose to a child that a donor was used (or might not do so) whether or not they have pre-existing social or family links to the donor. Parents might alternatively disclose that IVF was involved in the child's birth, but not disclose the fact of the gamete donation. For example, among a study of families who used 'genetic' or 'full' surrogacy (where the surrogate provides her egg as well as carrying the pregnancy) 76 per cent of the parents who had informed their child of the fact of the surrogacy had not disclosed the use of the surrogate's egg, although all said they would probably tell in the future.[161]

[159] Melissa Rippon responding to the Working Group's call for evidence.
[160] Andrea Williams responding to the Working Group's call for evidence.
[161] Readings J, Blake L, Casey P, Jadva V, and Golombok S (2011) Secrecy, disclosure and everything in-between: decisions of parents of children conceived by donor insemination, egg donation and surrogacy *Reproductive BioMedicine Online* **22**: 485-95.

4.103 Research is not available for the rates of disclosure of donor conception post-2005, when UK law removed anonymity for sperm and egg donors. This leaves a gap in our knowledge of the subject. However, in a study of children born in 2000 when donors were still anonymous, 40 per cent of children born by egg donation and 28 per cent of children born by sperm donation had been told of their donor conception by the time they had reached seven years old.[162]

4.104 In terms of the psychological impact of disclosure of assisted reproduction on the resulting children, including learning of the use of donated gametes, the available evidence indicates that earlier disclosure is likely to have a better outcome than disclosing this information later in the person's life. Studies show that children told of their donor conception in their preschool years were either curious or neutral about this disclosure at that time, but not distressed.[163] A study of the impact of disclosure of donor conception on the emotional adjustment of children found that children informed of their biological origins by the age of seven showed positive emotional adjustment.[164] The families who had disclosed the fact of donor conception were also found to show more positive parent-child relationships than the comparison group of non-disclosing families.

4.105 As part of a paper reviewing English-language peer-reviewed published journal papers on the perceptions and experiences of donor-conceived people who have learned the nature of their conception, UK researchers have looked at the desire of some of the participants in these papers to learn more about their gamete donor.[165] The reviewers concluded that: "Much of the available research evidence concerns individuals conceived through sperm donation conducted under a regime that promoted both [donor] anonymity and non-disclosure [of the fact of the gamete donation to the resulting child]. Consequently, there is little research that pertains to other forms of collaborative reproduction, such as oocyte [egg] donation... Nor is there much research involving individuals conceived under regimes in which early parental disclosure is both advocated and practised; where the donor's identity is accessible to donor-conceived individuals; where the identity of the donor is known to the recipient from the outset (as in donation between friends and family members); and regarding donor-conceived people's interests in learning about genetic relatives other than their donor. Furthermore, most studies have been of a cross-sectional nature, thus little of the existing research offers a longer-term perspective on individuals' experiences and perceptions as these develop throughout their lives."

4.106 With these caveats in mind, the Working Group noted that the review of papers indicated that more participants in studies were reported to be motivated to seek contact with their (usually, sperm) donor out of curiosity and a desire to know more about themselves, than because they had a desire to initiate a 'parent-child' relationship with the donor: "Most studies reported a desire of at least some participants to learn the identity of, and to make contact with, their donor. This was so as to satisfy their curiosity, to learn about their ancestry and medical history, and to provide a better understanding of their identity. In some instances this was expressed as a "right" rather than a merely a wish.[166] Where comparison between different family types was

[162] Golombok S, Readings J, Blake L *et al.* (2011) Children conceived by gamete donation: psychological adjustment and mother-child relationships at age 7 *Journal of Family Psychology* **25**: 230-9.

[163] Rumball A, and Adair V (1999) Telling the story: parents' scripts for donor offspring *Human Reproduction* **14**: 1392-9; Lindblad F, Gottlieb C, and Lalos O (2000) To tell or not to tell-what parents think about telling their children that they were born following donor insemination *Journal of Psychosomatic Obstetrics & Gynecology* **21**: 193-203; MacDougall K, Becker G, Scheib JE, and Nachtigall RD (2007) Strategies for disclosure: how parents approach telling their children that they were conceived with donor gametes *Fertility and Sterility* **87**: 524-33; Blake L, Casey P, Readings J, Jadva V, and Golombok S (2010) 'Daddy ran out of tadpoles': how parents tell their children that they are donor conceived, and what their 7-year-olds understand *Human Reproduction* **25**: 2527-34.

[164] Golombok S, Readings J, Blake L *et al.* (2011) Children conceived by gamete donation: psychological adjustment and mother-child relationships at age 7 *Journal of Family Psychology* **25**: 230-9.

[165] Blyth E, Crawshaw M, Frith L and Jones C (2012) Donor-conceived people's views and experiences of their genetic origins: a critical analysis of the research evidence *Journal of Law and Medicine* **19**: 769-89.

[166] Turner AJ and Coyle A (2000) What does it mean to be a donor offspring? The identity experiences of adults conceived by donor insemination and the implications for counselling and therapy *Human Reproduction* 15: 2041-51.

undertaken,[167] participants with single lesbian parents were more likely than those with single heterosexual parents to report a greater interest in establishing a relationship with their donor (and both of these were more likely to do so than those with two parents). Several studies reported that some participants wished not only to know their donor but to have a relationship with him. While the desired nature of this relationship was not articulated in any depth in any of the studies, rarely did this extend to wanting a parent-child relationship. In so far as motivations were explored, satisfying curiosity appeared to be commonly shared."[168]

4.107 Having examined some of the evidence around the views of donor-conceived people towards identifying and perhaps contacting their donor, the Working Group noted that reproductive gamete donation and mitochondrial donation would each be likely to involve different factors and be performed in different contexts. This could create important differences between the experiences of mitochondrial donor-conceived people and those of gamete donor-conceived people. The Working Group felt that these differences could be relevant to whether mitochondrial donors should be mandatorily required to be identifiable to the resulting people.

4.108 For example, reproductive gamete donation is sought above other alternative routes to parenthood by people who would value a genetic link to their child via themselves and/or their partner. These prospective parents may strongly prefer to experience carrying a pregnancy and giving birth to a child. They may either have medical problems affecting their fertility, or be seeking to avoid passing on a (nuclear or mitochondrial) genetic problem, or perhaps both partners are of the same sex, or there is no partner.

4.109 Much donor conception via UK licensed clinics takes place with donors not previously known to the recipients, whom they do not meet. In this arrangement, there is no intention that the donor will take part in parenting any resulting child, and the donor may not be aware of the outcome of their donation. Since the introduction of regulations in 2004 and a review of the HFEA's approach to information disclosure, those who donated after 1 August 1991 are entitled to request information from the HFEA about the number, sex and year of birth of any people born as a result of their donation.[169] If the donation took place before the implementation of the HFE Act 1990, donors can seek information available via the voluntary contact register UK DonorLink.[170]

4.110 Cell reconstruction therapies, by contrast, would only be requested in order to avoid the transmission of serious genetic disease and may not be accompanied by any fertility problem. The background context of a serious genetic disorder may have resulted in a range of physical and emotional effects on the part of the intending parents, previous children they have had and their wider families, which the resulting child may grow up to be keenly aware of. The child's nuclear genetic contributors will be their mother, and her male partner (or a sperm donor if required). The use of a sperm donor to make a nuclear genetic contribution does not bring up issues unique to cell reconstruction therapies and so we will not explore that in any detail. In the

[167] Beeson D, Jennings P and Kramer W (2011) Offspring searching for their sperm donors: how family type shapes the process *Human Reproduction* **26**: 2415-24.

[168] Mahlstedt P, LaBounty K and Kennedy T (2010) The views of adult offspring of sperm donation: essential feedback for the development of ethical guidelines within the practice of assisted reproductive technology in the United States *Fertility and Sterility* **93**: 2236-46; Scheib J, Riordan M and Rubin S (2005) Adolescents with open identity sperm donors: reports from 12 to 17 year olds *Human Reproduction* **20**: 239-52; Kirkman M (2004) Genetic connection and relationships in narratives of donor assisted conception *Australian Journal of Emerging Technologies and Society* **2**: 1-21; Vanfraussen K, Ponjaert-Kristoffersen I and Brewaeys A (2001) An attempt to reconstruct children's donor concept: a comparison between children's and lesbian parents' attitudes towards donor anonymity *Human Reproduction* **16**: 2019-25; Turner AJ and Coyle A (2000) What does it mean to be a donor offspring? The identity experiences of adults conceived by donor insemination and the implications for counselling and therapy *Human Reproduction* 15: 2041-51.

[169] HFEA (2012) Your rights and responsibilities as a donor – apply for information, available at: http://www.hfea.gov.uk/1975.html. See also HFEA Chair's letter (2004) CH(04)07, available at: http://www.hfea.gov.uk/2675.html; HFEA Ethics and Law Committee paper (2004) ELC (09/04) 01 http://www.hfea.gov.uk/docs/ELC_disclosure_Sept04.pdf.

[170] UK Donor Link is a voluntary organisation that helps facilitate contact between people affected by donation before 1991, and can match applicants using DNA testing. See: UK DonorLink (2012) *UK DonorLink homepage*, available at: http://www.ukdonorlink.org.uk/.

pronuclear transfer technique, the mitochondrial donor's egg will be fertilised by either the intending father or a sperm donor as necessary, before the resulting embryo is enucleated and his pronuclei discarded, so the Working Group will not further explore this temporary nuclear contribution.

4.111 The mitochondrial donor could be a female genetic relative of the intending mother who is suitable and willing to donate, or an unrelated donor who is either known, or unknown to the intending mother. The use of a mitochondrial donor may be of significance to the resulting person if they view genetic links as being particularly significant in regards to the creating social roles.

4.112 Having said that, the Working Group felt that where people do regard genetic links as signifying particular social relationships, it is possible that nuclear and mitochondrial genetic links may be viewed quite differently. It is beyond the remit of this project to fully investigate the widely variable perceptions of parenthood as brought about by genetic connections (or the lack of them). However, it does seem apparent to the Working Group that mitochondrial donation could be difficult to fit into some of the aspects often thought of as denoting characteristics of (nuclear) genetic 'parenthood'. These differences might affect perceptions of the social relationships that might be seen to be implied by a mitochondrial donation.

4.113 For example, paternal and maternal nuclear genetic contributions create a child with a unique nuclear genome, reflecting various recognisable aspects of these two genetic contributors. By contrast, it is discordant with current cultural conventions generated around (nuclear) genetic parenthood, that (as far as we are aware) mitochondrial genes convey to the resulting child no physical resemblances or other traits of personal characteristics of the donor, beyond that of health or ill-health. It is also discordant that mitochondrial genetic contributions (usually) create no identifying or distinguishable link between the resulting child, and their mother (or donor, in the case of cell reconstruction) and her mother, her brothers and sisters, maternal aunts and uncles and maternal grandmother. A gamete donor contributes 50 per cent of the child's unique nuclear genetic makeup, the full complement of the child's genetic contribution from either the maternal or paternal source. Taken alone, mitochondrial genes do not uniquely link the resulting child to their donor in the same way that a donation of nuclear genes would do, and may not give the child a mitochondrial genome distinguishable from those carried by several other close relatives on their donor's side.

4.114 The Working Group concluded that in societies where gamete donation, surrogacy and adoption are established and largely accepted it seems unlikely that any greater problems would result for children born after the donation of mitochondria. It has been stated by researchers studying donor conceived children, that as regards their psychological adjustment, children born through mitochondrial donation may be "much more like naturally conceived children, than donor conceived children."[171]The framing of regulation could have a key role in reflecting and in shaping the participants' expectations around the mitochondrial donor-child relationship, which might or might not fit with how donors or resulting people regard their experience, so this would need to be considered very carefully.

Cultural representations of mitochondria and their inheritance

4.115 Currently, it does not appear that any strong psycho-social or cultural emphasis is generally placed on mitochondrial inheritance as a specific element of personal identity. Indeed, in comparison to the widespread awareness of 'genes' and 'DNA' (usually implying nuclear DNA) in our culture, by contrast many people do not seem to be aware of the existence of mitochondria.

[171] Professor Susan Golombok, Director, Centre for Family Research, University of Cambridge (19 March 2012) Presentation to the Nuffield Council's Working Group: fact-finding meeting.

4.116 The Working Group has not found any expressions of a cultural concept of the mitochondrial 'family' in popular discourse, nor any widespread interest or emphasis on mitochondrial origins as a key part of personal identity. Professor Mary Herbert, a researcher of cell reconstruction techniques for the prevention of transmission of mtDNA disorders, alluded to this in responding to our call for evidence: "If ... mitochondrial genes conferred genetic identity, we would consider ourselves to be more closely related to our maternal grandmother than to our paternal grandmother. As this is not considered to be the case, it can be concluded that by the societal norms, mtDNA does not confer genetic identity."[172]

4.117 Having said this, a range of views have been expressed around the significance of mitochondrial inheritance in media discussion of the prospect of cell reconstruction techniques. These are demonstrated in the language used in some media headlines to describe the parentage of people who could be born if cell reconstruction procedures were permitted. Some journalists have heralded "three-parent embryos" and "three-parent babies" in discussing these techniques,[173] while others use the more nuanced "three-person IVF".[174] Other commentators have written in the media to compare aspects of the procedures to bone marrow donation, which also incorporates donor genes into patients' bodies.[175] Elsewhere, MST and PNT techniques have been described in the media as being like making structural repairs to functional objects, such as "changing the batteries in a laptop", or "changing the bacteria in our intestines", the provenance of which are not usually seen as having any resonance for social relationships.[176]

4.118 The Working Group noted that there is a specific section of society currently interested in the significance of mitochondrial inheritance, as seen in the online market for mitochondrial genetic testing. This is advertised to family historians as a means of gaining information connecting an individual's maternal line to specific population groups and possibly to their global geographic distribution.[177] While not a great deal is known about the perceptions of any social meaning signified by this information to the users of such tests, the information is offered as an adjunct to genealogical research, rather than as part of a process of discovering a central part of personal identity.

4.119 Genetic testing for genealogy has occasionally been represented in broadcast media, mostly focusing on genetics as a historical research tool, but sometimes augmented with personal stories in which mitochondrial testing is presented as information pertinent to personal and cultural identity. In 2003, in *Motherland: a genetic journey*, a one-off documentary made for the BBC, British people 'tracked down relatives' in contemporary Africa and the Caribbean using 'Y' chromosome and mitochondrial DNA tracing to explore their family history and the impact of the slave trade on families and individuals.[178] The programme used scientific methods taken from

[172] Professor Mary Herbert (University of Newcastle) responding to the Working Group's call for evidence.
[173] BBC News Online (5 February 2008) *Three-parent embryo formed in lab*, available at: http://news.bbc.co.uk/1/hi/health/7227861.stm; New Scientist (20 April 2011) *'Three-parent' IVF babies on their way*, available at: http://www.newscientist.com/blogs/shortsharpscience/2011/04/three-parent-babies-on-their-w.html; Mail Online (12 March 2011) *Babies with three parents and free of genetic disease could soon be born using controversial IVF technique*, available at: http://www.dailymail.co.uk/health/article-1365287/Babies-THREE-parents-born-years-controversial-IVF-technique-gets-ahead.html#ixzz1iaiH7Ylk.
[174] BBC News Online (19 January 2012) 'Three-person IVF' technique moves closer', available at: http://www.bbc.co.uk/news/health-16627043.
[175] BioNews (3 May 2011) *IVF and the prevention of mitochondrial DNA disease: the moral issues*, available at: http://www.bionews.org.uk/page_94023.asp.
[176] The Guardian (19 April 2011) *Scientists seek to implant embryos with genetic material from three parents*, available at: http://www.guardian.co.uk/science/2011/apr/19/scientists-embryos-three-parents; BBC News Online (26 August 2009) *Genetic advance raises IVF hopes*, available at: http://news.bbc.co.uk/1/hi/health/8220553.stm.
[177] See, for example, these commercial websites: Genetree.com (2012) *Mitochondrial DNA (mtDNA)*, available at: http://www.genetree.com/mtdna; Ancestry.com (2012) *Maternal lineage test*, available at: http://dna.ancestry.com/learnMoreMaternal.aspx; Rootsforreal.com (2012) *Your ancestral genetic line*, available at: http://www.rootsforreal.com/index.php; Family Tree DNA.com *Products and Pricing*, available at: http://www.familytreedna.com/products.aspx
[178] BBC Two (5 February 2003) Long lost roots of Black Britons revealed by groundbreaking BBC TWO, available at: http://www.bbc.co.uk/pressoffice/pressreleases/stories/2003/02_february/05/motherland.shtml.

archaeogenetics,[179] but an academic from this discipline argued that the programme-makers had overstated the specificity of information gained from mtDNA testing by introducing contemporary individuals to each other as 'relatives', on the basis of shared similarities of mtDNA. These similarities, he noted, can be found in many populations across different continents: "The powerful feelings evoked by ideas of ancestry were combined with intense emotions engendered by the memory of the Atlantic slave trade. And yet how could the geneticists be sure that Bioko was really the place that Beaula's lineage came from? Studies of human genetic diversity have barely begun. Yet the fashion for genetic ancestry testing is booming. [...] But what does it have to do with who we really are? The identity of African slaves was beaten out of them and had to be reforged. Geneticists do not hold the key to restoring it. Beaula McCalla met the Bubis of today, not the people of Bioko hundreds of years ago. To imagine how little the modern Bubis might have in common with their distant ancestors, we only have to consider how Europeans have changed since the slave trade. By tracking the history of genes back through time, geneticists can try to reconstruct the migrations and expansions of the human species. They have no special insight into ethnicity and identity. Geneticists – like preachers and philosophers before them – need to avoid promising more than they can deliver."[180]

4.120 More recently in the US, the PBS series *African American Lives* (2006), *Oprah's roots: an African American Lives Special* (2007) and the series *African American Lives 2* (2008), featured African-American celebrities exploring their family histories and ultimately tracing their mitochondrial 'roots' back to Africa and then visiting "an area where genetic, historical and anthropological evidence suggests the participant's ancestors lived."[181]

4.121 The Working Group notes that future generations could use the same testing services to trace their mitochondrial inheritance, if they should be minded to do so. If mitochondrial donation techniques had been used in their maternal line, there would be a point at which a donor's mitochondria would be seen to replace the previously-inherited mitochondria in the maternal line. Little is known about what personal meaning this knowledge would be likely to have for distant family members who have traced their maternal line back through generations. It is of course possible that in future, cultural attitudes may change towards the significance of mitochondrial DNA, as they have done regarding nuclear DNA over the preceding decades.

Concern for future generations and sex selection

4.122 Reproductive autonomy is a principle concerning the non-interference in reproductive decision-making. This could mean allowing potential parents to exercise freedoms in deciding if, when, how many, and to a limited extent 'what kind of' children they have. In practice this is subject to the law and regulation of each jurisdiction, and the resources and professional expertise available to prospective parents.

4.123 To deny potential parents access to novel treatments such as PNT and MST is to restrict the reproductive autonomy of those who wish to use their own gametes to have children and to avoid the birth of babies who may have disabling or life-threatening disorders.

4.124 Arguments for the limitation of reproductive autonomy in respect of novel treatments are often made on the grounds of safety for the child born as a result of a new procedure. In this case,

[179] A term which may be defined as 'the geographic distribution of modern human genetic variation, with the aim of addressing questions from archaeology, anthropology and history'. See: http://www.fbs.leeds.ac.uk/staff/profile.php?tag=Richards.
[180] *The Guardian* (21 February 2003) Beware the gene genies, available at: http://www.guardian.co.uk/education/2003/feb/21/highereducation.uk.
[181] PBS (2006) African American lives - introduction, available at: http://www.pbs.org/wnet/aalives/2006/about.html. See also: PBS (2008) African American lives 2, available at: http://www.pbs.org/wnet/aalives/ and GPB (2007) Oprah's Roots: an African American Lives special, available at: http://www.gpb.org/oprahs-roots.

this has been also been argued because PNT and MST would produce permanent changes into the germline of resulting children.

4.125 As distinct from nuclear genes, it is currently believed that only daughters born as a result of mitochondrial donation would be able to pass on their mtDNA to subsequent generations. Because of this, it has been proposed that prospective parents using these technologies should be able to use pre-implantation sex selection (preferring male embryos) if they requested it in order to limit the risks of transmitting any adverse side effects of the techniques to future generations. It has even been proposed that until more is known about the techniques only male embryos should be transferred to limit future transmission. It should be noted that even though it would be used for 'health related' reasons, the use of sex selection would not limit any potential health risks to the first generation of children born from PNT or MST as both sexes are equally likely to be affected should any problems inherent to cell reconstruction technique be passed on alongside the healthy donated mitochondria.

4.126 It is possible, therefore, that if a choice of healthy embryos is available, prospective parents might request sex selection, preferring to put back only male embryos as males could not pass on any mutated mitochondria to future generations of their family. Whether or not such medical problems eventuated, parents might also be concerned that daughters born after the use of novel techniques would also have to face difficult reproductive decisions about whether to use their own eggs to have children.

4.127 There are precedents to these issues of sex selection raised by PNT and MST. It has been argued that PGD for some sex-linked conditions might involve replacing only healthy males or only healthy females respectively, so as not to pass on the disorder to further generations. Although trans-generational risk is not of itself a licensable reason to undertake PGD, there are instances of certain genetic conditions where female carriers (known as 'manifesting carriers') can be affected, albeit mildly. In practice, where PGD identifies manifesting carriers in these circumstances, parental choice about embryo selection is noted, and their own or family members' experiences as a manifesting carrier might influence that decision.

4.128 Some commentators argue that because of the germline implications, if cell reconstruction technologies are permitted as treatments, only male embryos should be permitted for transfer until more information can be gathered about the techniques. This would prioritise the research information that would be able to be gathered from the male children born, but would exclude some potential parents who do not wish to use sex selection or could not produce any male embryos suitable for transfer from using the technologies. Dr Ken Taylor and Professor Erica Haimes responded to the Working Group's call for evidence to argue that it is not reasonable to create what, in their view, would be seen as an 'experimental' group of male children to permit prospective parents to use sex selection techniques to limit the risks of transmitting any unforeseen adverse side effects: "[It] would be unacceptable and render the children born 'experimental offspring' … the boys born would need to be monitored throughout their lives and deemed healthy before females could be conceived in this way: they would in effect be experiments. In suggesting that only males be conceived initially, there is an underlying assumption that the unknown long-term adverse consequences would relate only to the mitochondria (passed to the next generation through eggs, not sperm). As this may not be the case, there is no justification for limiting the risk to one particular sex. No technique for the eradication of disease should be permitted until there is reasonable evidence for its safety. We would not argue that experimental treatments should not be permitted in medicine, however… if such a course of action as selecting only males needs to be considered, it implies that at the time of offering the treatment too little is known about its safety. Another implication is that should sex selection be permitted the boys born from such treatment would live with uncertainty about their future health, beyond that normally experienced. The potential psychological implications of this would need to be included in pre-treatment counselling of the couples."[182]

[182] Response by Ken Taylor and Erica Haimes to the Working Group's call for evidence, paragraphs 3.1-3.3.

People living with mitochondrial disorders

4.129 Currently the laws around PGD do not consider the needs of subsequent generations as grounds for offering the procedures, and nor would PND be offered on any such basis of transgenerational interests, so sex selection on these grounds alone could not be offered without a change in regulation.

4.130 Another aspect of possible concern for future generations has been raised in respect of genetic interventions, opportunities for selection, and medical interventions more widely. This is the concern that introducing PNT and MST would have adverse practical and identity effects on the community of people already living with (in this instance) mitochondrial disorders. However, many believe that members of the family who have experience of the reality of living with the condition that may be tested for, prevented or improved by an intervention are the most appropriate judge of whether the condition is serious enough to take up the intervention that may be offered. While some impairments (for example deafness) have resulted in flourishing cultural communities with which some deaf people closely identify, we can assume that many people affected by mitochondrial disorders would feel that the negative effects of being born with a serious progressive disorder would be best avoided.

4.131 Some people also make the argument that allowing parents options to avoid disorders in their children does not imply negation of the equality of people living with that disorder either by those parents, or by wider society in allowing those interventions to be offered. The need for society's continued and improved support of disabled people to allow them to flourish can be seen as a separate aim which does not require the restriction of reproductive choice.

4.132 However, other people campaigning for better support and rights for disabled people perceive a conflict between these positions. They argue that harm is caused to disabled people by fewer people with impairments being born, and that the offence and hurt caused to disabled people by parents seeking to avoid or 'select out' births of children with the same disabling conditions is a reason not to permit technologies of this kind. In the *Telegraph*, columnist Cristina Odone comment: "Chemotherapy and vaccines are used to save lives – confirming that every one of them is special. The new technique [PNT] instead aims to save only healthy lives; and keep unborn the rest."[183]

4.133 The Working Group did not find any clear path from permitting elements of reproductive choice towards a lack of opportunities and negative effects on personal or community identity for disabled people, such that the proposed techniques might be seen as unethical to offer as treatments.

Other applications of the technologies

4.134 If PNT or MST were approved for treatment in a jurisdiction, and the techniques became accessible and acceptable to prospective patients, clinicians or patients might then ask to use the techniques for purposes other from the avoidance of the transmission of serious disease, or which have no therapeutic intention. This evolution in the demand for technologies beyond the purpose for which they were originally introduced has been seen with many medical treatments. In most parts of the world, and within many societies, wider access to assisted conception treatments will also depend on financial resources, raising issues of equity of access which are also beyond our remit to discuss.

[183] *The Telegraph* (20 Jan 2012) *The three-parent family: this is another attempt to dehumanise disabled people*, available at: http://blogs.telegraph.co.uk/news/cristinaodone/100131389/the-three-parent-family-this-is-another-attempt-to-dehumanise-disabled-people/.

4.135 When new assisted reproduction treatments are brought into treatment use, even for clear therapeutic reasons, there is often public and policy debate about unintended or unforeseen uses of the technology. This reflects complex and often contradictory societal attitudes towards conception, parenthood and new technologies. The motives of patients who might want to use such techniques, and of clinicians who might want to offer them, may be questioned. A further discussion of this is beyond our remit here, other than to note that the passage of time has offered little evidence of large numbers of individuals who are keen to undergo invasive treatments without compelling motivations for seeking to do so.

4.136 The Working Group has no reason to assume that research work is being undertaken into non-therapeutic uses of MST or PNT at this time. However, during discussions with the Working Group, researchers and bioethicists were able to think of other ways in which the techniques might be used, including for non-therapeutic reasons.

4.137 An example given of another therapeutic purpose was of the use of PNT and MST to 'rejuvenate' the eggs of women experiencing difficulty in conceiving using their own eggs (for example) because they were at the upper end of the reproductive age range. The proportion of mutated mitochondria tends to increase with a woman's age and this can hinder the general development of an embryo.

4.138 In such a scenario, the use of PNT or MST with donated mitochondria from a younger woman might allow the older woman to become pregnant (or to have a genetically-related child through a surrogacy arrangement). This was the drive, albeit in the absence of any experimental data, to the initial use of cytoplasmic transfer where mitochondria containing cytoplasm from younger women's eggs was added to infertile older women's eggs in the hope that the alteration in proportion might yield a therapeutic effect. If this theoretical use of PNT or MST were shown experimentally to be effective and safe for such a purpose, it could offer women reaching the end of their natural fertility the opportunity to have a genetic connection to a resulting child via the contribution of their nuclear DNA.

4.139 Here the intention is also to create a healthy baby who shares a nuclear genetic connection to its mother. If research showed no additional risks to mother or child beyond those accepted as inherent in using other forms of assisted conception to facilitate motherhood in older women, then this use of cell reconstruction technology would need to be considered on its own merits.

4.140 PNT and MST techniques could also potentially be used to allow a woman with a major genetic problem in her nuclear genes to create a genetic link with her child through the use of her mitochondria, without passing on nuclear DNA. The intending mother could use the mtDNA from her unfertilised egg or a zygote she had created with the pronuclei or the nucleus of an unfertilised egg contributed by a donor. This would prevent the transmission of a serious disease and create a genetic connection which was desired by the mother. This is obviously only a theoretical example, but if there were no safety reason against using the transfer technique in this way, then ethically it would seem to be as justified as using donated mitochondrial DNA to avoid serious genetic problems.

4.141 Another possible non-therapeutic use was mentioned in discussions. In this scenario there are no relevant medical problems, but a same sex couple might request PNT or MST because one partner wishes to have a genetic connection via mitochondria to their child, while the other partner will provide the child with nuclear DNA. There could be a range of scenarios in which a woman wishes to have a genetic link to a child and so requests the use of PNT or MST in order to create this link via her mitochondrial genes.

4.142 Many parents value a genetic connection to their children where this is possible to achieve. The theoretical request to use PNT or MST by two women and a man purely in order to achieve this genetic connection would not depart from that norm. Some ethical positions may privilege therapeutic uses of technologies to the extent that all non-medical uses are inadmissible. However if non-therapeutic uses may be considered, and are safe and effective, this type of request does not present any obvious ethical objections. Many assisted reproduction

techniques have been developed for the sole purpose of allowing parents to have children with whom they share a genetic connection, for example, ICSI versus use of donor sperm. Such requests may not initially be approved of by regulators or sanctioned by society, but attitudes may alter over time.

4.143 The Working Group noted that examples such as the one above of a woman requesting cell reconstructive technologies purely for the non-therapeutic purpose of creating a genetic connection, highlight the way in which medical technologies allow the separation of 'genetic parentage' from day-to-day parenting, and the importance most of us place on intentions to parent. A mitochondrial donor undertakes the same action as the same-sex (co-)mother in this example, but has different intentions regarding any parenting role in the child's life. However, we tend to view these two actions vary differently and to attribute very different social roles to these protagonists. The significance of the same genetic link can thus be emphasised or minimised, depending on the circumstances and preferences of the adults involved, and we expand traditional kinship models accordingly to accommodate new technologies.

4.144 The privileging or minimisation of the genetic link depending on different family circumstances long precedes the advent of reproductive technologies. Throughout history conventions have grown up to present the outward appearance of combined social and genetic parenting. Relatively recent examples include the practice of 'closed' adoption, or where stepfathers legally adopted the children of women from her previous relationships so that her children could carry his surname. Today, however, family structures created on the basis of an intention to parent are ordinary. Arrangements that reflect a separation of social and genetic parenting such as stepfamilies, or families formed by open adoption, are commonplace and no longer stigmatised. This can be seen in the widespread use of unambiguous descriptive terms for these relationships such as 'step-parent' or 'adoptive parent' and 'birth parent'. However this is not the case for all parents and some will prefer to be open only about aspects of the family structure which accord with traditional family structures, and choose to minimise or conceal those which are discordant with their personal family or kinship ideology.[184]

4.145 In terms of the practical likelihood of cell reconstruction therapies ever being available in the UK for non-therapeutic reasons, we do not envisage this being put into place in the foreseeable future. Even if the regulation-making powers (in their current form) written into the HFE Act 1990 were brought into effect, PNT and MST would only be permitted to be used for preventing mitochondrial disorders. No other therapeutic uses (such as to treat infertility) would be permitted by these powers, and nor would, for example, the sole treatment aim of creating a mitochondrial genetic connection between people who would otherwise have no genetic link.

Increased need for egg donors

4.146 One of the major barriers mentioned by scientists when assessing the potential for cell reconstruction techniques to become treatments is the fact that many more egg donors will need to be found to undertake the research required in order for the safety and efficacy of PNT and MST to be established, and if therapies are to be provided in future. A shortage of egg donors is an acknowledged problem in respect of donation for reproduction, and it is not yet clear whether egg donors would be more likely to come forward in sufficient numbers to take part in mitochondrial donation for research or treatment use.

4.147 Care will need to be taken that both mitochondrial donors known to the recipients and 'altruistic' donors are recruited and supported appropriately. There is already HFEA guidance in place for informing and supporting egg donors for research and reproduction prior to seeking their consent, and we would regard this as a model to follow for mitochondrial donors.

[184] Ragoné H, and Ragsurp H (1994) *Surrogate motherhood: conception in the heart* (San Francisco: Westview Press).

4.148 In reproductive gamete donation in settings such the UK, where donors are required to be identifiable by people born from their donation, limits are placed on donations. For clinics and recipients to create an unlimited number of children from the same donor is seen as discordant with the kinship norms behind policies aiming to ensure that donor-conceived people can have contact with their donor (should they wish to). Limits are also imposed on the number of times a donor can donate, or (as in the UK) on the number of families one donor can donate to, because of fears of incestuous relationships being unwittingly formed between donor half-siblings. The HFEA specifies that no more than ten families can use the same gamete donor (and the donor may specify a lower limit) because "for psychological reasons, a limit should be placed on the number of possible siblings that a donor-conceived person could expect to have. There is also a perception that a higher family limit would risk two genetically related siblings entering into a relationship without knowing they were related (although the actual risk of this remains very low)."[185]

4.149 We do not consider it appropriate for a regulator to set a limit on the number of times a mitochondrial donor can donate eggs for research or reproduction, other than to protect her from repeated ovarian stimulation. Suitability for egg donation is a matter for clinical discussion between the individual woman and her doctor at any time, and whether or not she goes ahead should depend on the medical advice she has received and on her wishes. In contrast to the very small likelihood of relationships between biological half-siblings after reproductive gamete donation, very many of us already share types of mitochondria that originated from the same very distant ancestral origins, with no ill effect.

Status of the human embryo

4.150 Research in the UK and US to develop cell reconstruction techniques has involved the creation, manipulation and destruction of human and animal embryos. If PNT and MST are approved as treatments in the UK, human embryos will be manipulated and destroyed as part of the treatment process. Further embryo research is also likely to be conducted in connection with PNT and MST in order to investigate the effectiveness of PGD in gathering information about mitochondrial DNA mutations in reconstructed embryos.

4.151 The Working Group does not have the remit to investigate the moral status of the embryo. The starting point for the Working Group's deliberations is where UK law stands, that embryos have a special moral status, but under specified conditions may be used in research and the treatment of patients. As maternal spindle transfer is performed on unfertilised eggs, we have not specifically considered ethical issues around the status of the embryo with regards to that technique. Our discussion relates largely to pronuclear transfer.

4.152 The Working Group adopted the position of UK law in considering the zygote at pronuclear stage to be an embryo. The fertilised egg at pronuclear stage is not universally regarded as an embryo however, because the genetic material in the two pronuclei has not yet fused together to form the cell nucleus. For example, Article 8 of the German Embryo Protection Act 1990 states: "In terms of the law, an embryo is defined as the fertilised, viable human egg cell from the point of pronuclear fusion, or any totipotent cell extracted from an embryo that is, under the necessary requirements, capable of dividing and of developing into an individual".[186]

4.153 There tend to be three broad ethical positions in regards to embryo research, which may be varied in specific circumstances. These tend to range from requiring no ethical prohibitions on the use of embryos because they are not accorded any specific moral value, to a 'gradualist' position that accords the embryo increasing moral significance as it develops and possibly requires it to be protected after a certain stage. This is behind the 14-day developmental limit on

[185] Human Fertilisation and Embryology Authority (14 July 2011) *HFEA agrees new policies about family donation and the number of families one donor can create*, available at: http://www.hfea.gov.uk/6518.html.
[186] German Reference Centre for Ethics in the Life Sciences (2010) *The German Embryo Protection Act 1990*, available at: http://www.drze.de/in-focus/stem-cell-research/modules/the-german-embryo-protection-act?set_language=en.

research on human embryos in the UK. The gradualist approach is seen also in much of the legislation affecting pregnancy (after the embryo has implanted in the womb). The third position prohibits any creation, use or destruction of embryos in research, because embryos are considered to have equal moral status to born people, often from the point of fertilisation of the egg. This special status may be linked to the embryo's potential to become a person, invoking the need for society to protect its integrity whether or not the embryo is in the womb, or likely to be. This view opposes human embryo research, assisted conception and abortion, seeing the only legitimate actors on the outcome of embryos to be nature or chance (or a divine power). This also applies when foregoing human interference on embryos would mean that children would be born with worse outcomes than if research involving embryos had been used to avoid this eventuality, or that without research having been performed on human embryos, some subsequent children would not be able to be born at all.

4.154 The Christian Medical Fellowship responded to the call for evidence to say that: "None of the safety concerns [around PNT or MST] will be able to be answered without research on hundreds, if not thousands, of human embryos, all of which will be destroyed in the process. We question the justification for the destruction of hundreds of human embryos that have already been destroyed in this research and the many more that will be destroyed in the future. We do not consider that the hunt for 'therapies" that might prevent a small number of disabled children (with mitochondrial disease) being born justifies the destruction of hundreds if not thousands of embryonic human lives."[187]

4.155 It should be noted that other assisted reproductive technologies likely to be used with this patient group also destroy embryos: for example, PGD with embryo selection. PGD determines genetic information about IVF embryos *in vitro* via cell biopsy. If suitable healthy embryos can be identified via PGD, usually selected from a greater number produced by the couple, one or two will be made available for transfer to the woman's uterus. Additional 'spare' healthy embryos not selected for transfer may be transferred in future after being frozen storage, but if not used they will be discarded. The embryos found to be unsuitable for transfer will be destroyed immediately. This might involve the whole selection of embryos produced. This process may occur over repeated IVF/PGD cycles if no embryos suitable for transfer are found. It may be noted that the PNT and MST processes do not create any such 'spare' embryos.

4.156 The UK Transhumanist Association ("a growing movement that affirms the desirability of improving the human condition by developing technology"), responded to the call for evidence to say that: "Both [MST and PNT] would raise fewer ethical concerns than preimplantation genetic screening, if they imply the creation, and subsequent destruction, of fewer embryos."[188]

4.157 The Working Group agreed that, with the appropriate oversight, research that may destroy or alter eggs or embryos (and which may develop treatments which require the same), is justifiable in seeking to prevent serious genetic illnesses being transmitted. This is particularly pertinent to this particular patient group in view of the limited alternative options available to affected families.

4.158 The Medical Research Council and the Wellcome Trust submitted to the call for evidence that: "It has been argued that the two techniques currently in question could raise different ethical issues and so one or other should be prioritised for scientific investigation. The nature of science is such that avenues to explore both techniques need to remain open so that the efficacy and safety of each technique can be compared. Furthermore, exploration of each

[187] Christian Medical Fellowship, responding to the Working Group's call for evidence, at paragraph 3.15.
[188] UK Transhumanist Association, responding to the Working Group's call for evidence, at paragraph 5.

technique has and will lead to insights into mitochondria and developmental biology which will benefit other areas of research."[189]

4.159 The Working Group did not find that human embryo research in respect of either PNT or MST, nor the prospect of either as an eventual treatment, appears to be ethically preferable to the other, and did not find any ethical barriers to the investigation of both techniques. To conduct research involving the use and destruction of human embryos in respect of both techniques seems likely to be required in order to establish which (if either) procedure may be most likely to offer an acceptably safe and effective means of avoiding the transmission of mtDNA disorders whilst allowing patients to use their own eggs. We also note that UK law and regulation already reflect the principle of only using human embryos in research to a level that has been found to be necessary and desirable.

[189] The Medical Research Council and the Wellcome Trust, responding to the Working Group's call for evidence, paragraph 5.

Chapter 5

Conclusions and issues for further consideration

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5.1 Many affected people responding to the call for evidence said that they would welcome an opportunity for themselves, or for others affected by similar conditions, to use their own gametes to have children. They stated that they would also like to be able to expect that their children, and future generations of their family, could be born without the risk of inheriting the mitochondrial problems that have affected others in the family.

5.2 In light of the health and social benefits to individuals and families living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children, the Working Group believes that, if the PNT and MST techniques are proven to be acceptably safe and effective, on balance it would be ethical for families wishing to use them to do so. This should, however, be subject to the offer of an appropriate level of information and support.

5.3 If the proposed therapies are adequately shown to be safe and effective and patients choose to use them, the Working Group believes that, potentially, these could be of benefit to both prospective parents and the resulting children who might be born free from mitochondrial disorders. This health benefit appears to be likely to extend to descendants of any women born via these therapies, although this would not ordinarily be the primary objective of the treatment.

5.4 Given the above and subject to the appropriate oversight, we believe that, as a research objective, it is ethical to gather further information about PNT and MST in order that they can be considered for treatment use. Neither research in respect of PNT, nor in respect of MST, appears to us to be ethically preferable to the other, and to conduct both is likely to be necessary in order to establish which, if either, is most likely to offer an acceptably safe and effective treatment.

5.5 The Working Group has noted that many objections to germline interventions are of a generic nature, applying equally well, or not at all, to both mitochondrial and nuclear transfer or nuclear modifications. As we have indicated in this report, it has not escaped our notice that any Parliamentary authorisation of treatments that would include changes to the mitochondrial genome would be seen by some as creating a ‘slippery slope’ towards the approval of comparable interventions made in the nuclear genome, were these to be proposed in future. It is our view that the clear material difference between mitochondrial and nuclear genes means, in practice, that the adoption of PNT or MST would not necessitate the adoption of nuclear transfer or nuclear modification technologies if they were to emerge in future. It would be possible for appropriate further regulation to be put in place, were this seen as necessary. However, it is neither our intention nor part of our remit to comment on the desirability of the adoption of nuclear transfer or nuclear modification technologies, except to say that these would have to be judged separately and on their own merits.

Treatment as part of a research trial

5.6 We believe that in the first instance that PNT and MST (or any comparable future treatment) should only be offered as part of a research trial in centres specialising in mitochondrial disorders. Consent to follow up would need to be included as a mandatory part of parental consent to participating in the trial.

Parentage of the child

5.7 Although the perception of the personal and social relationships created by egg or embryo reconstruction would remain a matter for the individuals concerned, it is the view of the Working

Group that 'motherhood' is not indicated either biologically or legally by virtue of mitochondrial donation.

5.8 For the reasons specified in our discussion, the Working Group do not believe that it is accurate to refer to the mitochondrial donor as a 'mother' or 'third parent' to the child. It is disappointing that, for example, some media coverage has presented this an inherent part of these prospective treatments.

Regulation: counselling

5.9 The Working Group would wish to see protection and promotion of the autonomy of the various parties that may be affected by the introduction of these techniques. This may require additional stipulations beyond current safeguards on matters such as counselling and information for couples and donors. At present those seeking licensed assisted reproduction treatments in the UK are offered, under the HFE Act, ''proper'' information and a ''suitable opportunity to receive proper counselling about the implications''[190] of the treatment. If introduced, the provision of cell reconstruction treatments should follow this model.

5.10 However, the Working Group notes that in practice the quality of counselling for existing specialist procedures such as PGD can vary. Given the complex nature of mitochondrial inheritance and the issues of novelty around reconstructing embryos, the Working Group suggests that while the initial discussions about the procedure could be within a routine setting, there should be a further opportunity offered for prospective parents to speak to a specialist in a dedicated unit accustomed to dealing with mitochondrial disorders. This specialist would have received appropriate training and have up-to-date information available in order to discuss patients' options with them. The same level of specialist involvement is also required in the existing provision of PND around mitochondrial disorders and should be offered to inform and support patients as far as possible in the decisions that they make.

Regulation: follow-up

5.11 Researchers have strongly recommended that if, in the future, families use cell reconstruction techniques, they should commit to allowing very long-term follow-up of their children and families over generations in order to further knowledge about the outcomes of these techniques. This aim is to be strongly endorsed. However, this expectation may prove difficult to fulfil on the part of both families and the research community over several decades, and previous experience has shown only patchy success in this aim in regards to other newly-introduced assisted reproductive techniques. The voluntary nature of the research relationship can make it difficult to anticipate what level of short or long-term follow up data may be feasibly gathered from families.

5.12 To support this aim, the Working Group would recommend the creation of a centrally-funded register of any such procedures performed in the UK, maintained and kept for a length of time that is deemed appropriate, and accessible to researchers over several decades.

Regulation: status of the mitochondrial donor

5.13 The status of the mitochondrial donor in regulation should be carefully considered by Parliamentarians and regulators, particularly where this may bring with it implications for the perception of the potential social relationships engendered by the donation. While women undergoing a procedure in order to donate mitochondria would also be egg donors, in this

[190] HFEA (2012) *Counselling: the offer of counselling*, available at: http://www.hfea.gov.uk/345.html#guidanceSection3600.

instance their intention is solely that the relevant parts of their egg should be used in the reconstruction of another egg or embryo for the avoidance of genetic disease.

5.14 Accordingly, the Working Group does not take the view that the donor of mitochondria should be given the same status in all aspects of regulation as a reproductive egg or embryo donor. Differences would include that we do not believe mitochondrial donors should be mandatorily required to be identifiable to the adults born from their donation. Similarly, we see no reason for the regulator to establish sibling registries of the kind that would contain the details of mitochondrial donors or the resulting people and are intended to enable those born using the mitochondria of the same donor to contact each other. We do not see the need for a regulatory limit to be placed on the number of families to whom a mitochondrial donor could donate, which should be a matter for discussion between the woman and her doctor. However, we believe that other aspects of the current regulation and safeguards for egg donors should be applied equally to mitochondrial donors, including the number of times that they receive ovarian stimulation drugs for this purpose and in respect of financial compensation.

5.15 Should mitochondrial donation techniques be permitted for treatment use in future, it might be that a voluntary system for contact between mitochondrial donors and the resulting people is set up and mediated by an appropriate central body. Voluntary activity of this kind would offer the maximum flexibility to donors and the resulting people if they wished to become identifiable to each other or to make contact.

Regulation: status of different sperm donors involved in mitochondrial donation

5.16 If a sperm donor were used to fertilise the egg of an intending mother in order to contribute the male pronucleus as part of the PNT technique, or if he fertilised a reconstructed egg after MST has been performed, then he should be treated like any other reproductive sperm donor by regulations.

5.17 However, the regulatory position is less clear to us if, for some reason, a sperm donor were solely used to fertilise the egg of the mitochondrial donor in order to create an embryo used as part of PNT. The status of the sperm donor in this instance should be carefully considered by Parliamentarians and regulators as this may bring with it implications for the perception of the potential social relationships engendered by the donation. While men giving sperm would also be sperm donors, in this instance their intention would be solely that the nuclear material in their sperm would be used to create an embryo containing healthy mitochondria, and for that embryo then to be enucleated and their nuclear material discarded.

5.18 The Working Group does not take the view, therefore, that this category of sperm donor should have the same status in regulation as a sperm donor for reproduction, or a donor used to fertilise a reconstructed egg after MST, or a donor in PNT where his sperm creates a pronucleus that would contribute to the nucleus of the embryo.

5.19 We believe this category of sperm donor should be treated differently in regulation in some specific aspects including, for example, that he should not be required to be mandatorily identifiable to the adults born from his donation, nor be subject to a regulatory limit on the number of families to whom he could donate for the purpose of fertilising an egg of a mitochondrial donor that is to be enucleated.

Long term safeguarding of treatment register data

5.20 Assurances will need to be obtained from the Department of Health that funding can be made available in the long term for a national treatment register. This could require Government to make a commitment that would endure over several decades. We would be concerned if a commitment was not available for sustained funding to retain the details of mitochondrial donors and the resulting people.

Further issues for discussion

5.21 The Working Group's remit and timescale for producing this report were limited in order to allow a timely contribution towards the wider policy discussion of PNT and MST that will take place in 2012 and beyond. However, we feel that the wider policy debate could benefit from a fuller discussion of the ethics of different kinds of prospective and theoretical germline therapies. This would include potential therapies that would act on the cell nucleus with heritable effects, and therapies which might involve nuclear transfer in its various forms. The ethical robustness and sustainability of policy decisions made around cell reconstructive therapies and other potential treatments for serious genetic disorders would benefit from a thorough discussion of the full range of these other prospective treatments.

Appendices

Appendix 1: Method of working

The Council aimed to produce a report which would further public discussion and debate by identifying and examining ethical issues relevant to novel techniques to prevent the transmission of inherited mitochondrial DNA disorders.

Accordingly, the Council appointed a Working Group consisting of three Council members and three experts in related fields, and the project began on 4 November 2011. Over the course of the project the Working Group held three meetings to discuss project business, identify the main issues, and outline areas for the project to investigate and the process by which this should be done. Then five fact-finding sessions were held at which the Group heard presentations from various invited speakers in person and via videoconferencing (listed in Acknowlegments)

A public Call for Evidence began on 19 January 2012. Respondents were asked to send written submissions of no more than 2,000 words in length by 24 February 2012.[191] This was an open call for evidence, seeking ethical views on any aspect of these emerging techniques and the issues associated with them. Structured questions for response were not provided, but a note was provided of key ethical questions which the Working Group was likely to consider. Background information was also provided by the Council in support of the Call for Evidence. 92 responses were received, to be placed on the Council Website after the publication of the report, subject to respondents' permission.

A subgroup of four Council members assisted the Project Leader with the drafting of the report by providing comments before and after the full Council was invited to approve the draft report. Two external experts were also invited to give comments on the draft (listed in Acknowledgments). The report was published on 12 June 2012.

[191] Details are available at: http://www.nuffieldbioethics.org/mitochondrial-donation.

Appendix 2: Call for evidence

Method

The call for evidence ran from 19 January to 24 February 2012. The timing allowed the project to capitalise on public interest in issues around novel techniques to prevent the transmission of inherited mitochondrial disorders, as announcements from the Department of Health and the Department for Business, Innovation and Skills, and also from the Wellcome Trust were made on the same day. Respondents were asked to send written submissions of no more than 2,000 words in length by 24 February 2012.[192]

This was an open call for evidence, seeking ethical views on any aspect of these emerging techniques and the issues associated with them. Accordingly, structured questions for response were not provided, but a note was made of key ethical questions which the Working Group was likely to consider. Background information was provided in support of the call for evidence, which received 92 responses.

The original call for evidence is available on the Council's website, and individual responses will also be published in full on the website, where respondents have granted permission for the Council to do so.[193] The responses received played an important role in shaping the Working Group's thinking, and the Working Group is very grateful to all those who contributed.

List of respondents to the call for evidence

There were 77 responses from individuals and 15 responses from organisations; 27 respondents requested not to be listed as respondents.

Individuals

Dr Elizabeth Allan
Professor Brenda Almond, Emeritus Professor of Moral and Social Philosophy, University of Hull
Kemal Altug
Carolyn Appleby
Mrs Catherine Binyon
Mrs Louise Blair
Lynn Byron
K. Cairns
George Chisholm
Pat Chisholm
Joanne Cullen
Dr Rebecca Dimond, Cesagen, Cardiff University
Rachel Dolan
P. J. Egerton
Mrs Margaret Evans
Carol Gordon
Lauren Griffiths
Mrs Sylvia Halliday
Professor Mary Herbert, Newcastle University
Maria Hood
Elena Horder
A. Maguire

[192] Details are available at: http://www.nuffieldbioethics.org/mitochondrial-donation.
[193] See: http://www.nuffieldbioethics.org/mitochondrial-donation.

Professor Calum MacKellar, Centre for Bioethics and Emerging Technologies, St Mary's University College, Twickenham
Onyema Montanya
Alison Murdoch, Newcastle Fertility Centre @ Life
Sylvia Nixon
Mr Roy Parkinson
Melissa Rippon
Noreen Russell
Jolene Sharp
Louise Smith
Brian Somerville
Ken Taylor and Erica Haimes, PEALS (Policy, Ethics and Life Sciences) Research Centre, Newcastle University
Valerie Thomas
Isobel Tripney
Professor Doug Turnbull, Newcastle University
Oliver Wilkes
Mrs Andrea Williams

Organisations

Anscombe Bioethics Centre, Oxford
Association of Medical Research Charities and Muscular Dystrophy Campaign
British Fertility Society
British Medical Association
Samantha Byerley, on behalf of the ACE Executive Committee
CARE
Christian Medical Fellowship
Comment on Reproductive Ethics (CORE)
Genetic Alliance UK
H+ UK (the UK Transhumanist Association)
Erica Haimes and colleagues, PEALS (Policy, Ethics and Life Sciences) Research Centre, Newcastle University
Humanist Society of Scotland
Medical Research Council and Wellcome Trust
Progress Educational Trust
Wales Gene Park and ESRC Cesagen

Appendix 3: Working Group members' short biographies

Geoff Watts (Chair)

Dr Geoff Watts is Chair the Council's Working Group on mitochondrial donation and is a member of the Nuffield Council on Bioethics. He spent five years in research before becoming a science and medical writer and broadcaster. He presented BBC Radio 4's Medicine Now and, more recently, its science programme Leading Edge. He was a founder member of, and served for six years on, the Human Genetics Commission.

Peter Braude

Peter Braude is Emeritus Professor of Obstetrics and Gynaecology at King's College London, where he was Head of the Department of Women's Health, and directed the Centre for Preimplantation Genetic Diagnosis for the Guy's and St Thomas' NHS Foundation Trust. Peter has been involved in assisted reproduction and embryo research in Cambridge and London for over 30 years. He was a member of the HFEA (1999–2004), Chair of the RCOG Scientific Advisory Committee (2004–2007), and Chair of the Expert Advisory Committee to the HFEA on Multiple Birth after IVF. He was a member of the HFEA core panel that reviewed scientific methods to avoid mitochondrial disease, which reported to the Secretary of State for Health in 2011.

Frances Flinter

Frances Flinter is Professor of Clinical Genetics at King's College London, and Consultant in Clinical Genetics at Guy's & St Thomas' NHS Foundation Trust. She trained in Paediatrics and Genetics and has a special interest in Pre-implantation Genetic Diagnosis (PGD) and inherited renal disease. She has been involved with the PGD Programme at Guy's & St Thomas's since its inception. Frances was Clinical Director of the Evelina Children's Hospital (2000–2007), member of the Human Genetics Commission (2005–2012) and former President of the Clinical Genetics Society (2009–2011).

Sian Harding

Professor Sian Harding is Professor of Cardiac Pharmacology at the National Heart And Lung Institute, a Division of the Faculty of Medicine, Imperial College London, as well as a member of the Nuffield Council on Bioethics. She is also a Member of the Central Ethical Review Committee for Animal Studies and Stem cells for Safer Medicines. Scientific interests include gene and cell therapy for heart disease.

Tim Lewens

Dr Tim Lewens is a Reader in Philosophy of the Sciences, Department of History and Philosophy of Science, and Fellow of Clare College, University of Cambridge and is a member of the Nuffield Council on Bioethics. He was Co-Chair of the Cambridge Bioethics Forum 2002-2010. His primary research interests are the philosophy of biology, philosophy of science and bioethics.

Michael Parker

Professor Parker is the Director of the Ethox Centre at the University of Oxford, which researches ethical and social issues arising in collaborative global health research. He directs the Global Health Bioethics Network, which builds ethics capacity and carries out ethics research in collaboration with the Wellcome Trust Major Overseas Programmes in Kenya, Thailand, South Africa, Viet Nam, and Malawi. Since 2001, he has co-ordinated the UK Genethics Club, a national ethics forum for genetics professionals to discuss the ethical issues arising in their day-to-day practice.

List of abbreviations

AC	Appeal Committee (of the HFEA)
ARTs	assisted reproductive technologies
BMA	British Medical Association
CF	cystic fibrosis
CORE	Comment on Reproductive Ethics
CT	Cytoplasmic transfer
CVS	chorionic villus sampling
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
HFEA	Human Fertilisation and Embryology Authority
ICSI	intra-cytoplasmic sperm injection
IVF	in vitro fertilisation
MELAS	mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MST	maternal spindle transfer
mtDNA	mitochondrial DNA
NARP	neurogenic muscle weakness, ataxia, retinitis pigmentosa
NT	nuclear transfer
PDD	pervasive developmental disorder
PGD	preimplantation genetic diagnosis
PND	prenatal diagnosis
PNT	pronuclear transfer
rRNA	ribosomal ribonucleic acid
SCNT	somatic cell nuclear transfer
tRNA	transfer ribonucleic acid
UNESCO (IBC)	United Nations Educational, Scientific and Cultural Organization (International Bioethics Committee)

NUFFIELD COUNCIL ON BIOETHICS

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