# ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

## A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

19 April 2018

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## About the Bioethics Advisory Committee

*The BAC is an independent advisory committee that was established by the Government in December 2000 to address the ethical, legal and social issues arising from human biomedical research and its applications. BAC studies emerging areas in human biomedical research, and develops and recommends policies to the government as appropriate, with the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise its full potential for the benefit of mankind.*

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# ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

## CONSULTATION PAPER

### INTRODUCTION

1. In 2005, the Bioethics Advisory Committee (BAC) recommended in its *Genetic Testing and Genetic Research* Report that the clinical practice of germline genetic modification should not be allowed, pending further scientific evidence of its feasibility and safety.[1] In light of recent scientific developments and international debates on germline modification techniques for the prevention of mitochondrial genetic disorders, the BAC is reviewing its position on germline modification, with a focus on mitochondrial genome replacement technology.

2. To ensure its deliberations are comprehensive, the BAC would like to invite comments on whether or not the clinical application of mitochondrial genome replacement technology should be permitted in Singapore for the prevention of heritable mitochondrial disorders. All feedback provided will be taken into consideration by the Committee. You are welcome to respond to the questions raised in this consultation paper, and / or raise any other important issues that have not been covered.

3. The consultation paper is divided into three chapters :

   - Chapter 1 : Introduction to Mitochondrial Disorders;
   - Chapter 2 : Germline Modification for Mitochondrial Disorders; and
   - Chapter 3 : Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology

4. Information on how to send in your feedback, and a respondent's form, can be found on pages 27 and 28, respectively.

[1] Bioethics Advisory Committee, Singapore. *Genetic Testing and Genetic Research,* November 2005, Recommendation 12. BAC defined germline genetic modification as 'a type of gene technology that involves the alteration of a person's genetic makeup in a manner that is permanent and can be transmitted to his or her offspring' (para 4.51).

## Chapter 1 : Introduction to Mitochondrial Disorders

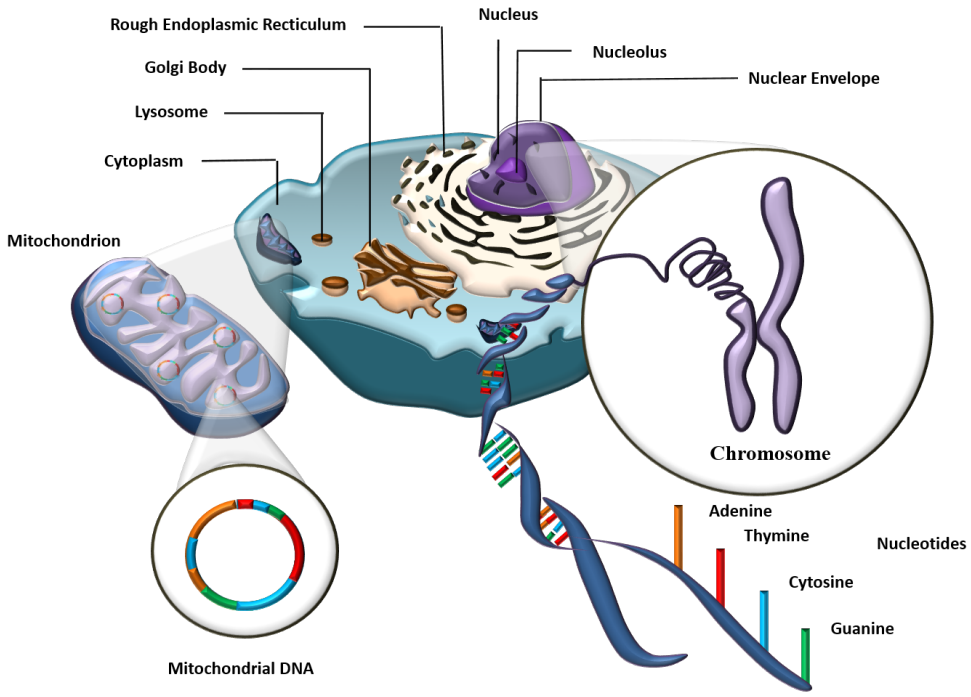
### Basic Genetic Concepts

5. Inherited traits are passed down from parent to child through complex biochemical molecules composed of deoxyribonucleic acid (DNA).

6. Most of the cell's DNA can be found within the nucleus of our cells. This is called the nuclear genome, which contains between 20,000 and 22,000 protein-coding genes. Genes are segments of the DNA sequence that code for inherited traits such as height and eye colour, blood type, muscle mass and the risk of developing of certain diseases. The DNA in the nucleus is organised into chromosomes. Most healthy human beings have 23 pairs of chromosomes — one set from the mother and another set from the father.

7. A small amount of the cell's DNA is found outside of the nucleus within tiny organelles in the cytoplasm of the cell known as mitochondria (singular: mitochondrion). This is called mitochondrial DNA (mtDNA) and it constitutes the mitochondrial genome which is made up of 37 genes, 13 of which are directly involved in the cell's energy production. The remaining 24 genes are involved in the production of mitochondrial proteins. mtDNA is inherited only from the mother and not the father, as the sperm does not contribute any mitochondria to the fertilised egg.[2] Unlike the nuclear DNA which is organised into linear chromosomes, mtDNA is organised as a circular loop. Each mitochondrion has several copies of mtDNA, and there are thousands of mitochondria within a cell.

**Figure 1.1 : Nuclear and Mitochondrial DNA**
(Figure not drawn to scale. Modified from : http://www.majordifferences.com/2015/05/difference-between-mitochondrial-dna.html#.WKvkFj_2OUl)




[2] Sperm cells contain mitochondria in the midpiece (or the base of the sperm head) to power the sperm's tail for movement. Following fertilisation, paternal mitochondria are destroyed, and mtDNA is only inherited from the mother. In contrast, nuclear DNA is inherited from both the mother and the father.

8. An important function of mitochondria is to provide energy for cells through a process called aerobic respiration. The metabolic pathway responsible for energy production in the mitochondrion is known as the respiratory chain. The respiratory chain comprises five enzyme complexes that reside on the inner mitochondrial membrane, where electron transfer and proton translocation generate an energy storing molecule, adenosine triphosphate (ATP). mtDNA codes for only 13 of the approximately 90 proteins of the respiratory chain, the rest being coded by the nuclear DNA.

**Clinical Burden of Heritable Mitochondrial Disorders**

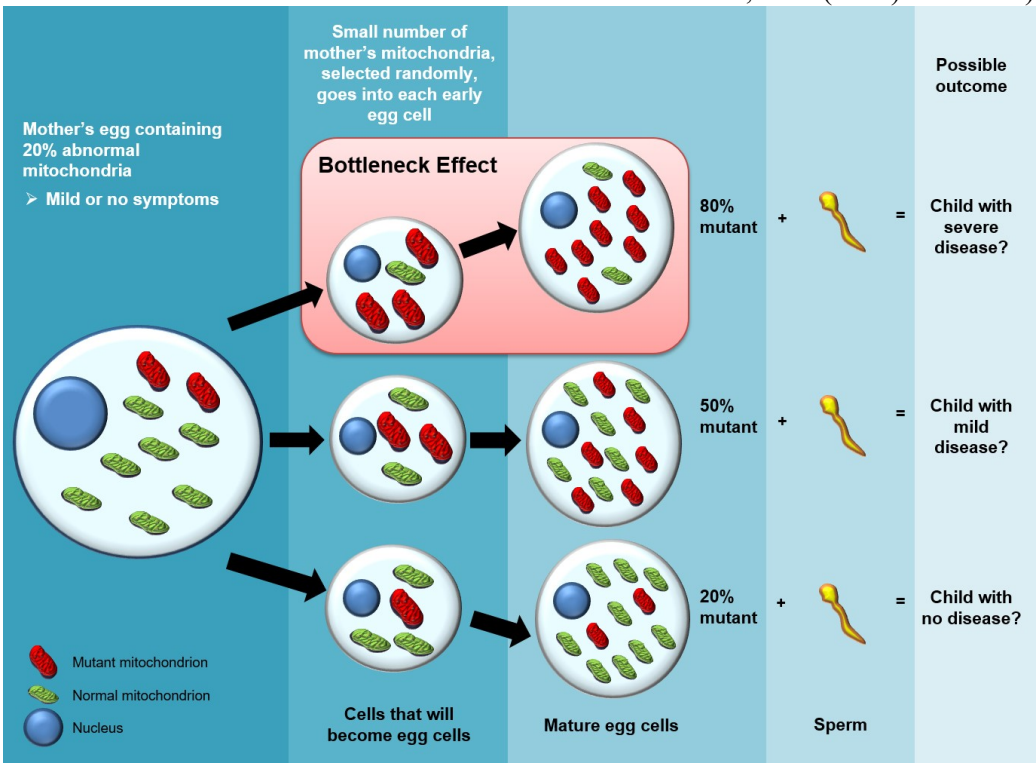
9. Mitochondrial disorders therefore can arise from anomalies in either the mitochondrial or nuclear genome. Although the mitochondrial genome is very small relative to the nuclear genome,[3] abnormalities in mtDNA can have debilitating and disabling effects given the mitochondrion's central role in cellular energy production. Disorders arising from mitochondrial dysfunction affect a range of highly energy-dependent organs and tissues including the brain (encephalopathy), muscle (myopathy), heart muscle (cardiomyopathy), inner ear (deafness), and endocrine system (e.g. diabetes). The symptoms and severity vary widely amongst patients, depending on the amount of abnormal compared to normal mtDNA — i.e. the relative ratio of dysfunctional and functional mitochondria in the cell — and the energy demands of the affected organ(s).

10. When all copies of the mtDNA in a cell are identical, this state is known as homoplasmy. It is rare, but possible, for individuals to have a homoplasmic population of abnormal mtDNA. Such homoplasmy usually causes serious health problems, leading to an early death.

11. A cell is heteroplasmic if it contains a mixture of normal and abnormal mtDNA. Some degree of heteroplasmy will exist in most persons because of defects in replication and maternal inheritance of abnormal mtDNA. The proportion of abnormal to normal mtDNA determines whether the person is likely to manifest any symptoms, as well as the range and severity of symptoms and age of onset. Generally, the higher the load of abnormal mtDNA, the more likely symptoms will manifest; but the absolute proportion will vary with the specific mutation. Different mtDNA mutations have different threshold levels of abnormal mtDNA load which are more likely to produce symptoms. For example, a child may have a mutation that causes early onset of movement disorder, developmental delay and seizures, even though the abnormal mtDNA load is very low. The relationship between abnormal load and symptoms varies between different tissues and different types of mitochondrial mutations, and different individuals may tolerate the same abnormal load differently.

[3] The mitochondrial genome contains 16,569 base pairs, while the nuclear genome has about 3,200,000,000 base pairs.

**Figure 1.2 : Maternal Inheritance of Mitochondrial DNA Mutations**
(Figure not drawn to scale. Modified from : Taylor RW & Turnbull DM. Mitochondrial DNA Mutations in Human Disease. *Nature Reviews Genetics*. 6, no. 5 (2005): 389–402.)




12. Healthy heteroplasmic female carriers with a low proportion of abnormal mtDNA may nevertheless have children with serious health problems. This occurs because of a phenomenon known as the "mitochondrial bottleneck". As the distribution of normal to abnormal mitochondria varies between cells, the proportion of abnormal mitochondria that may be present in each egg as it develops in the ovary may be different. If, by chance, mitochondria containing high levels of abnormal mtDNA populate the egg that is eventually fertilised, the result is a higher load, or even homoplasmy of abnormal mitochondrial genome in the resulting child (see Figure 1.2). This leads to a disease state. The chance of this phenomenon occurring increases with increasing loads of abnormal mtDNA in the mother's cells.

13. Presently, the prevalence of heritable mitochondrial diseases in Singapore has not been studied. As there is no significant racial or ethnic predilection for mitochondrial diseases, it is likely that population studies done in other countries can be extrapolated to Singapore. In the UK, it has been estimated that approximately 1 in 4,300 people suffer from inheritable mitochondrial disease, of which the minimum prevalence rate for mitochondrial disease caused by mtDNA mutations is 1 in 5,000.[4] However, because of the wide range and varying severity of symptoms, it is thought that the prevalence of mitochondrial disorders is likely to be higher than current estimates mainly due to a lack of recognition leading to under-diagnosis or misdiagnosis.

[4] Gorman G *et al*. Prevalence of Nuclear and Mitochondrial DNA Mutations related to Adult Mitochondrial Disease. *Ann Neurol*. 77 (2015) : 753-759.

**Treatment for Mitochondrial Disorders**

14. There is currently no cure for mitochondrial disorders, though many symptoms are treatable. Existing treatments include transplantation (liver or bone marrow transplant), specific medications, special diets and / or avoidance of triggers. However, these treatments vary in efficacy. In instances where treatment is ineffective or unavailable, medical management of these patients is mainly supportive, and is aimed at preventing or slowing down known complications of their condition.

**Preventing Transmission of Mitochondrial Disorders**

15. The risk of transmitting mitochondrial disorders due to mtDNA mutations can be complex and difficult to predict. The risk depends on the specific mutation, proportion of abnormal mtDNA carried by the affected woman, bottleneck effect and random distribution of mitochondria during egg production.

16. Currently, women carrying abnormal mtDNA who wish to have healthy children without the risk of developing mitochondrial disease may consider the following options : (1) adoption; (2) *in vitro* fertilisation using healthy donor eggs; (3) pre-implantation genetic diagnosis; and (4) prenatal diagnosis. However, these options are not always ideal due to certain difficulties and limitations, which are outlined below.

*Adoption*

17. Adoption is a long-standing option for couples who, for various reasons, cannot conceive their own child. However, there is a long waiting list for adoption in Singapore, and adopting a foreign child has become more difficult as countries have imposed more stringent criteria to clamp down on the illegal sale of babies.[5] Also, an adopted child will most likely not be genetically related to the prospective parents.

*In vitro fertilisation (IVF) using healthy donor egg*

18. This involves the fertilisation of a healthy donor egg with the husband's sperm and implantation of the resulting embryo in the prospective mother. Although the risk of transmitting mitochondrial disorders is eliminated, the child will not be genetically related to the mother unless the egg from a close relative is used. However, maternal relatives are often unsuitable donors as they may carry the same abnormal mtDNA.

*Pre-implantation genetic diagnosis (PGD)*

19. In PGD, cells are removed from early stage embryos created by IVF to test for the presence of gene mutation(s). Healthy embryos are then selected for implantation into the prospective mother. PGD is possible for families with nuclear DNA mitochondrial disorders as most of these conditions are autosomal

[5] Tan T. "Number of adoptions falls by half since 2014". *The Straits Times*. 12 May 2013. http://www.straitstimes.com/singapore/number-of-adoptions-in-singapore-falls-by-half-since-2004. (Accessed March 26, 2018)

recessive disorders and the presence of gene mutations is clearly predictive of disease. For women with mitochondrial disorders caused by defective mtDNA, PGD can be used by heteroplasmic women to select for embryos with no or a low load of abnormal mtDNA (which are unlikely to be symptomatic), but is not useful for women with a high load of abnormal mtDNA or with a homoplasmic population of abnormal mtDNA as all their eggs (and thus embryos) will carry a high load of mtDNA.

20. In heteroplasmic women for whom PGD may be feasible, there are some uncertainties about the reliability of PGD in preventing the transmission of mitochondrial disorders. Firstly, there may not be a close correlation of mutation load with disease severity in some mitochondrial mutations; secondly, there may not be a uniform distribution of mtDNA mutations in all the cells of an embryo — a natural phenomenon known as mosaicism; and thirdly, it is uncertain if (and how) an embryo's mutation load will change prenatally and postnatally. Studies have indicated that the levels of abnormal mtDNA may increase significantly during foetal development, such that selecting an embryo with a low proportion of abnormal mtDNA may not guarantee long-term health of the child.[6] This phenomenon, known as "reversion", is still poorly understood. Finally, PGD may also be ethically objectionable as it inevitably involves the destruction of human embryos deemed unsuitable for implantation.

*Prenatal diagnosis (PND)*

21. PND involves the testing of a foetus during pregnancy to check for the presence of gene mutation(s). This could be done during the late first trimester via chorionic villus sampling, or during the second trimester via amniocentesis. If the foetus is found to carry the mutation, the couple may choose to carry out elective pregnancy termination. Similar to PGD, PND is only useful for heteroplasmic women to reduce (though not eliminate) the risk of transmitting mitochondrial disorders to future generations. PND is also ethically contentious as it may lead to the elective termination of pregnancy.

[6] Mitalipov S *et al*. Limitations of Preimplantation Genetic Diagnosis for Mitochondrial DNA Diseases. *Cell Reports.* 7 (2014) : 935-937; and Wolf D *et al*. Mitochondrial Genome Inheritance and Replacement in the Human Germline. *EMBO Journal*. 36, no. 15 (2017) : 2177-2181.

## CHAPTER 2 : GERMLINE MODIFICATION FOR MITOCHONDRIAL DISORDERS

22. Germline modification occurs when a gene(s) in a germ cell (sperm or egg) or an early embryo is altered. As all cells of an individual are developed from the fertilised egg, any genetic modification introduced into the egg, sperm or early embryo is likely to appear in the genome of all cells in that individual's body. These altered genes may be passed down to future generations through that individual's gametes.

23. Hence, a potential application of germline modification is to prevent the transmission of inheritable genetic diseases in subsequent generations. While germline modification may be beneficial for diseases caused by a single abnormal gene, it is unlikely to be helpful for complex diseases such as diabetes mellitus where a combination of multiple genes and environmental factors contribute to the disease.

### Mitochondrial Genome Replacement Technology (MGRT)

24. Due to the limitations of existing alternatives mentioned in the preceding chapter, germline modification techniques are being explored for preventing mitochondrial disorders.[7] MGRT seeks to replace abnormal mitochondria with normal mitochondria through either egg (oocyte) or one-cell embryo (zygote) manipulation. This paper will discuss three techniques, namely Maternal Spindle Transfer (MST), Pronuclear Transfer (PNT) and Polar Body Transfer (PBT).

25. As short-term pre-clinical studies of MST and PNT conducted in mice and non-human primates had not suggested that the techniques were unsafe for use in humans, MST and PNT were approved by the UK Parliament in 2015 for clinical use to reduce the risk of transmitting serious mitochondrial disease. MGRT is only permissible in defined circumstances where the mother's eggs have a particular risk of having mitochondrial abnormalities caused by mtDNA; and there is a significant risk that a person with such abnormalities will develop serious mitochondrial disease.[8] For women who fulfil these two criteria, PGD is unlikely to work due to high heteroplasmy or homoplasmy of abnormal mtDNA.

26. Although PBT has not been legalised for clinical application in the UK, an expert scientific panel convened by the UK Human Fertilisation and Embryology Authority (HFEA) had identified it as a potentially 'simpler and safer' technique than MST and PNT.[9] The panel also concluded upon a review of the available scientific evidence, that PBT, like MST and PNT, was not unsafe. As such, this consultation paper reviews these three techniques for preventing the transmission of mitochondrial disorders.

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7 Though BAC considers MGRT to be a form of germline modification, there are important differences between MGRT and other germline therapies that alter the nuclear genome. The distinctions are discussed in detail in paragraph 76 of this paper.

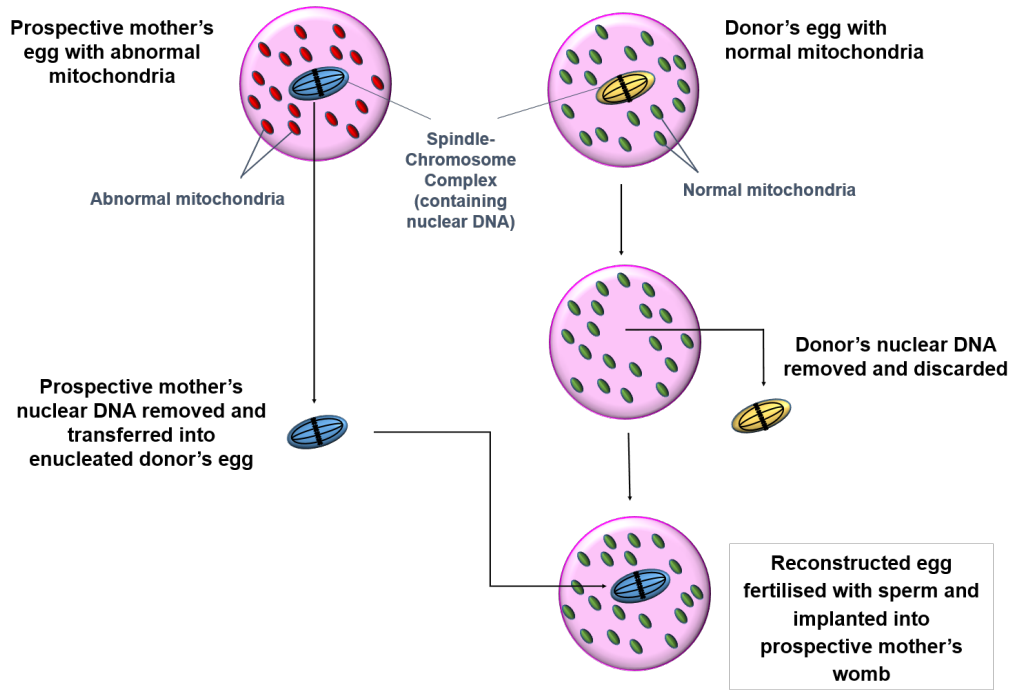
8 UK *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*. Regulation 5.

9 HFEA, UK. *Review of Safety and Efficacy of Polar Body Transfer to Avoid Mitochondrial Disease : Addendum to 'Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2014 Update*. October 2014. See p27.

*Maternal Spindle Transfer (MST)*

27. In MST, two eggs are involved in the process : one containing abnormal mitochondria from the prospective mother, and another containing normal mitochondria from a healthy donor. The maternal chromosomes, which are held together by a protein scaffold in a structure called the spindle-chromosome complex, are removed from the prospective mother's egg and transferred into the donor's healthy egg from which the donor's spindle-chromosome complex was previously removed. The reconstructed egg, which consists of the prospective mother's nuclear DNA and normal mitochondria from the donor's egg, is then fertilised. The resulting zygote is implanted into the prospective mother's womb.

**Figure 2.1 : Maternal Spindle Transfer (MST) in Eggs**
(Figure not drawn to scale. Modified from : Nuffield Council on Bioethics, UK. *Novel Techniques for Prevention of Mitochondrial DNA Disorders : an Ethical Review*. 2012.)




*Pronuclear Transfer (PNT)*

28. In PNT, both the prospective mother's egg (containing abnormal mitochondria) and the donor's egg (containing healthy mitochondria) are first fertilised with the father's sperm. After fertilisation, the two pronuclei[10] from the prospective parents' zygote are isolated and inserted into the donor's zygote from which its pronuclei were previously removed. The reconstructed zygote is then implanted into the prospective mother.

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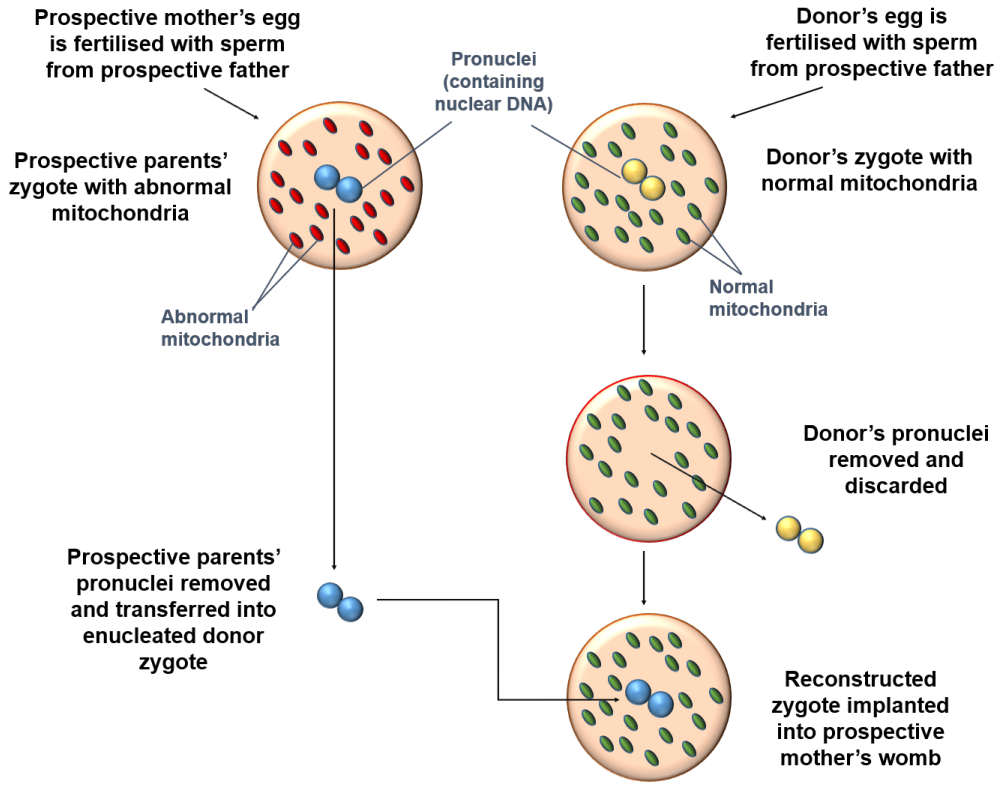
10 The two pronuclei — one pronucleus from the sperm, and one from the egg — are structures visible in the egg from about 10 hours after penetration by the sperm at fertilisation. Each contains the father's and mother's transmitted genetic material respectively, before they fuse to form a zygote ready for division to the two-cell stage.

**Figure 2.2 : Pronuclear Transfer (PNT) in One-Cell Embryonic Stage / Zygote**
(Figure not drawn to scale. Modified from : Nuffield Council on Bioethics, UK. *Novel Techniques for Prevention of Mitochondrial DNA Disorders : an Ethical Review.* 2012.)

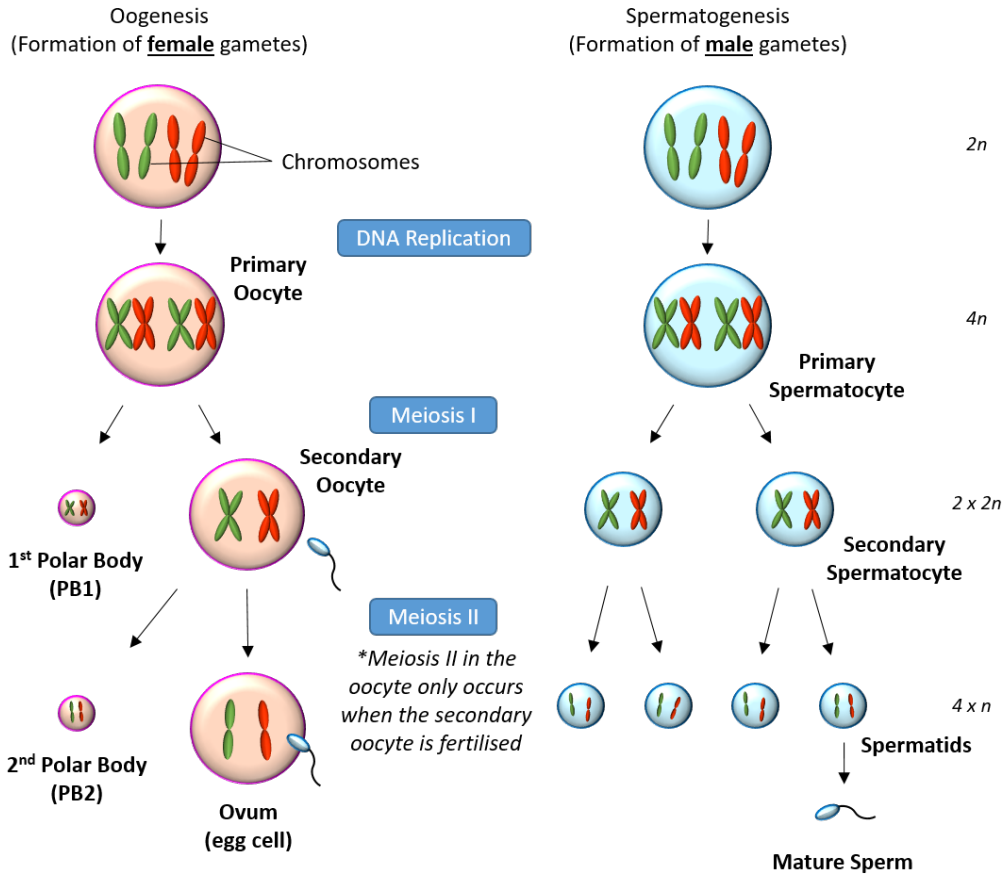



*Polar Body Transfer (PBT)*

29. Polar bodies are small cells that are produced during oogenesis — the formation of eggs — and fertilisation. Each polar body contains the same number of chromosomes as an egg's nucleus, but it has very little cytoplasm and hence few mitochondria, if any. This makes them ideal candidates for MGRT as it greatly reduces the chance of carrying over abnormal mtDNA into the donor's oocyte. In humans, polar bodies normally do not become fertilised or undergo further development, and would eventually disintegrate.

30. An immature developing egg cell undergoes two divisions which ultimately result in four mature egg cells, each having half the number of chromosomes (haploid) of normal body cells (diploid) [see Figure 2.3]. In males, each immature sperm cell (spermatocyte) produces four equal sized mature sperm. In females, each of the divisions produces cells of unequal sizes although half the chromosomes go to each cell during each division. The first division produces a maturing egg cell (secondary oocyte) and a much smaller cell, the first polar body (PB1). Both the maturing egg cell and PB1 contain the same number of chromosomes. PB1 generally disintegrates early during development. The next division occurs just after the sperm has entered the secondary oocyte and produces another smaller cell, the second polar body (PB2). Like PB1, PB2 also contains very little cytoplasm. However, PB2 contains half the number of chromosomes usually found in a body cell — just like the pronucleus of the mature egg (ovum).

**Figure 2.3 : Formation of Polar Bodies During Meiosis**
(Figure not drawn to scale and has been simplified for ease of understanding. Modified from : http://bodel.mtch.org/OnlineBio/BIOCD/text/chapter33/concept33.1.html)




31. There are two PBT techniques — PB1T and PB2T (see Figures 2.4 and 2.5). In PB1T, the nuclear DNA of the donor's unfertilised egg is replaced with the first polar body from the prospective mother's unfertilised egg; in PB2T, the maternal pronuclear DNA of the donor's fertilised egg is replaced with the second polar body from the prospective mother's fertilised egg. The resulting egg / zygote thus possesses normal mitochondria from the donor but genetic material from the prospective parents.

32. There are some possible advantages of PBT over MST and PNT, which include :

(i) reduces abnormal mtDNA carry-over to the child as the polar body contains very little cytoplasm and therefore few cellular organelles such as mitochondria;

(ii) reduces the risk of leaving chromosomes behind as all nuclear DNA is enclosed within the polar body;

(iii) does not require cytoskeletal inhibitors for removal of spindle or pronuclei from the patient's unfertilised or fertilised egg, thereby avoiding the attendant risks of using such inhibitors; and

(iv) involves the use of conventional micro-manipulation procedure that reduces the risk of damage, and increases efficiency.

**Figure 2.4 : Polar Body 1 Transfer (PB1T)**
(Figure not drawn to scale. Modified from : HFEA, UK. *Review of Safety and Efficacy of Polar Body Transfer to Avoid Mitochondrial Disease : Addendum to Third Scientific Review of Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2014 Update*. October 2014.)

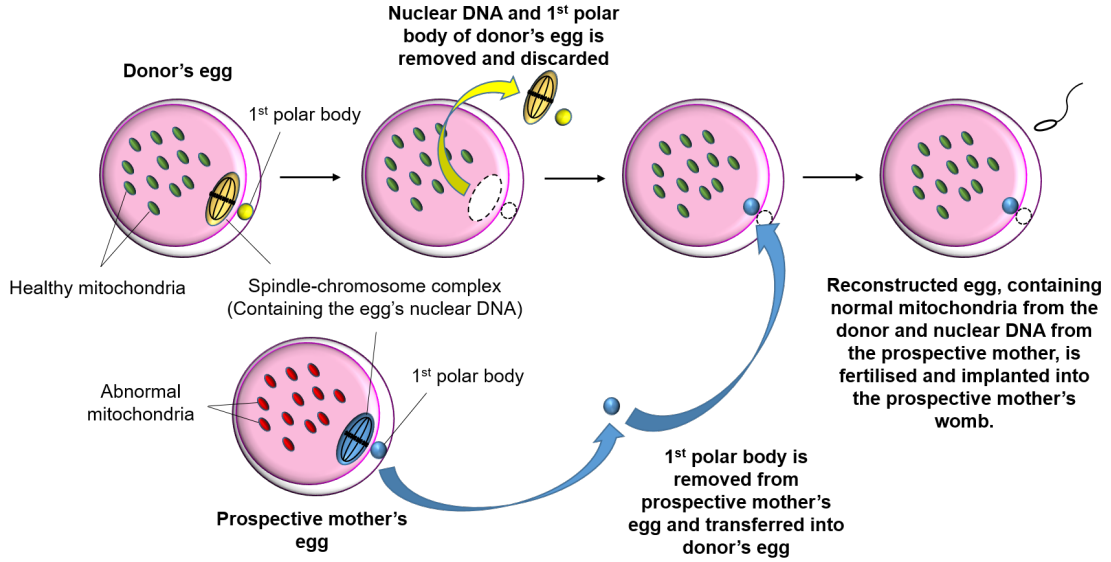
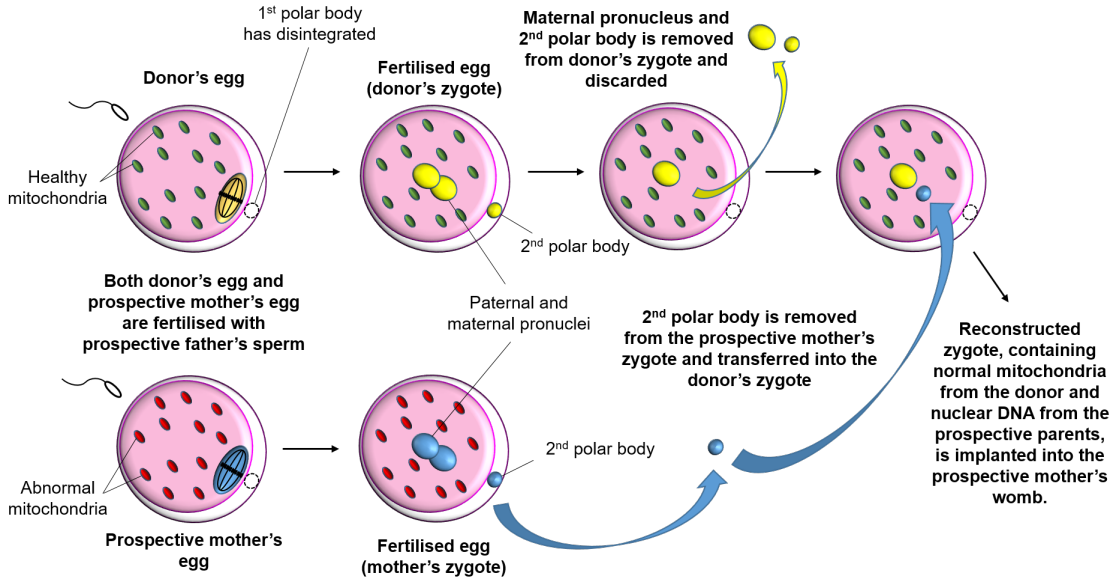



**Figure 2.5 : Polar Body 2 Transfer (PB2T)**
(Figure not drawn to scale. Modified from : HFEA, UK. *Review of Safety and Efficacy of Polar Body Transfer to Avoid Mitochondrial Disease : Addendum to 'Third Scientific Review of Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2014 Update*. October 2014.)



## International Scientific Developments

*MST*

33. In 2009, a research group led by Dr Shoukrat Mitalipov at the Oregon Health and Science University successfully produced four healthy male rhesus macaque monkeys using the MST technique,[11] proving the feasibility of the technique. A three-year follow-up study on these monkeys showed normal growth and development, and no detectable abnormalities.[12]

34. The potential feasibility of MST in preventing the transmission of abnormal mtDNA has also been demonstrated in human eggs.[13] In September 2016, a US research team led by Dr John Zhang from the New Hope Fertility Center in New York City announced the live birth of the world's first baby created through MST in Mexico.[14] The mother, a 36-year-old Jordanian woman who carried mtDNA known to cause Leigh syndrome, had four previous pregnancy losses and two deceased children from the disease. The doctors reported that the seven-month old boy had about 2% to 9% of abnormal mtDNA, was healthy thus far, and will be closely monitored with a long-term follow-up plan.[15] This live birth seems to provide proof-of-concept that MST can successfully reduce the risk of the transmission of serious mitochondrial disorders, but long-term follow-up of the child is essential to confirm that the level of abnormal mtDNA remains stable, and to ascertain safety.

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11 Tachibana M *et al.* Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells. *Nature.* 461 (2009) : 367-372.

12 Tachibana M *et al*. Towards Germline Gene Therapy of Inherited Mitochondrial Diseases. *Nature.* 493 (2013) : 627-631.

13 *Ibid.* See also : Paull D *et al*. Nuclear genome transfer in human oocytes eliminates mitochondrial DNA variants. *Nature.* 493 (2013) : 632-637.

14 Hamzelou J. "Exclusive : World's first baby born with new "3 parent" technique." *New Scientist.* 27 September 2016. https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/ (Accessed March 26, 2018). Dr John Zhang subsequently presented his research at the 2016 Scientific Congress of the American Society for Reproductive Medicine on 19 October 2016. An abstract of the presentation was published in *Fertility and Sterility* : Zhang J *et al.* First Live Birth using Human Oocytes Reconstituted by Spindle Nuclear Transfer for Mitochondrial DNA Mutation causing Leigh Syndrome. *Fertility and Sterility*. 106 (2016) : e375-e376.

15 Zhang J *et al*. Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease. *Reproductive Biomedicine Online.* 34 (2017) : 361-368.

*PNT*

35. PNT resulting in the live birth of normal offspring was first carried out successfully in mice in the early 1980s.[16] Its potential use to reduce the risk of transmitting mitochondrial disorders has since been illustrated in a mouse model carrying a large-scale deletion of its mtDNA,[17] as well as in abnormally[18] and normally[19] fertilised human zygotes that were created through routine IVF. Although pre-clinical research with MST has produced encouraging results, comparable success with PNT has not been reported in rhesus macaque monkeys.[20] In 2016, Dr John Zhang and team published a case study from 2003 in which a 30-year-old woman with unexplained infertility underwent PNT.[21] The procedure resulted in a triplet pregnancy with foetal heartbeats, but none of the foetuses survived despite a clinical reduction of the pregnancy to twins, and premature delivery of the remaining two.[22] It was not clear if the failed pregnancy was due to the genome manipulations or to the clinical management of the high-risk pregnancy. Nevertheless, analysis of the foetuses' red blood cells showed no detectable presence of abnormal mtDNA from the mother, suggesting that PNT could potentially prevent the transmission of mitochondrial disorders.

36. On 5 January 2017, a Ukrainian team led by Dr Valery Zukin reported that they had successfully delivered a baby girl who was conceived with the help of PNT.[23] The baby's mother had been suffering from infertility, and sought treatment from Dr Zukin and his team in order have a baby that was genetically related to her. Another baby boy, also conceived through PNT, was successfully delivered on 19 February 2017 by another mother.[24] Both babies were reported by the clinic to be healthy, though there have been no updates about their status since.[25]

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16 McGrath J & Solter D. Nuclear Transplantation in the Mouse Embryo by Microsurgery and Cell Fusion. *Science.* 220 (1983) : 1300-1302.

17 Sato A *et al.* Gene Therapy for Progeny of Mito-mice Carrying Pathogenic mtDNA by Nuclear Transplantation. *Proceedings of the National Academy of Sciences.* 102 (2005) : 16765-16770.

18 Craven L *et al*. Pronuclear Transfer in Human Embryos to Prevent the Transmission of Mitochondrial DNA disease. *Nature.* 465 (2010) : 82-85.

19 Hyslop LA *et al*. Towards Clinical Application of Pronuclear Transfer to Prevent Mitochondrial DNA Disease. *Nature.* 534 (2016) : 383-386.

20 HFEA, UK. *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2014 Update*. June 2014.

21 Zhang J *et al*. Pregnancy Derived from Human Zygote Pronuclear Transfer in a Patient who had Arrested Embryos after IVF. *Reproductive BioMedicine Online.* 33 (2016) : 529-533.

22 Foetal reduction was performed at 33 days after transfer, and the other two foetuses were lost at 24 and 29 weeks, following premature rapture of membrane and cord prolapse respectively.

23 Coghlan A. "First baby born using 3-parent technique to treat infertility". *New Scientist*. 18 January 2017. https://www.newscientist.com/article2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/ (Accessed March 26, 2018)

24 Coghlan A. "Questions raised over 3-parent baby procedure last year". *New Scientist.* 3 April 2017. https://www.newscientist.com/article/2126512-questions-raised-over-3-parent-baby-procedure-last-year/ (Accessed March 26, 2018)

25 *Ibid.*

*PBT*

37. To date, PBT studies have been conducted on mice[26] and human eggs.[27] As recent studies have indicated that reversion could be significant in MST and PNT,[28] PBT has become a promising alternative. Unlike the maternal spindle-chromosome complex and pronuclei, polar bodies are surrounded by very little cytoplasm and hence few or even no mitochondria. PBT results in a lower carryover of abnormal maternal mtDNA[29] and therefore a lower likelihood of reversion.

**MGRT Research in Singapore**

38. The BAC is not aware of the conduct of any MST, PNT, or PBT research on human embryos in Singapore.

**International Position on Germline Modification**

39. The BAC is guided in its deliberations by the principle of sustainability, which implies that we have a responsibility to our future generations, and that we should not jeopardise or prejudice their welfare. This principle has also been enshrined as "Article 16 – Protecting future generations" of the 2005 Universal Declaration on Bioethics and Human Rights, which states that : "The impact of life sciences on future generations, including on their genetic constitution, should be given due regard."[30]

40. The BAC had therefore, in its 2005 Report on *Genetic Testing and Genetic Research,* recommended a moratorium on germline genetic modification in clinical practice due to a serious concern that germline modification could have "potentially great impact on future generations".[31] The BAC was of the view that the clinical application of germline genetic modification should not be allowed until substantial research has been conducted to establish its feasibility and safety.

41. The National Medical Ethics Committee (NMEC) made a similar recommendation on germline gene therapy in its 2001 *Ethical Guidelines for Gene Technology*. Some of the ethical concerns raised by the NMEC were : uncertainty over its long-term safety and risks, the inadvertent selection against and elimination of alleles from the human gene pool that may benefit humans in potentially unknown ways, and the tenuous line between germline gene therapy and eugenics.[32]

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[26] Wang Tian *et al.* Polar Body Genome Transfer for Preventing the Transmission of Inherited Mitochondrial Diseases. *Cell*. 157 (2014) : 1591-1604.

[27] Ma H *et al.* Functional Human Oocytes Generated by Transfer of Polar Body Genomes. *Cell Stem Cell*. 20 (2017) : 112-119.

[28] Wolf D *et al*. Mitochondrial Genome Inheritance and Replacement in the Human Germline. *EMBO Journal*. 36, no. 15 (2017) : 2177-2181.

[29] Wu KL *et al.* Polar Bodies are Efficient Donors for Reconstruction of Human Embryos for Potential Mitochondrial Replacement Therapy. *Cell Research*. 27, no. 8 (2017) : 1069-1072.

[30] UNESCO. *Universal Declaration on Bioethics and Human Rights.* 2005. Article 16.

[31] Bioethics Advisory Committee. *Genetic Research and Genetic Testing*. 2005. Paragraph 4.52.

[32] National Medical Ethics Committee, Singapore. *Ethical Guidelines for Gene Technology.* 2001.

42. The moratorium on the clinical application of germline modification, which was recommended by both BAC and NMEC, is consistent with the stance taken internationally. The clinical practice of germline modification has been rendered unlawful by many countries, including Australia, Canada, Japan and Germany. An overview of various countries' positions is provided in Annex A.

43. In the 1997 UNESCO *Universal Declaration on the Human Genome and Human Rights*, germline interventions were identified as practices that could be contrary to human dignity.[33] This position was reiterated when the UNESCO International Bioethics Committee (IBC) reviewed the subject in 2003.[34] Reflecting on the subject again in 2015, the IBC recommended a moratorium on genome editing of the human germline, due to concerns about safety and its ethical implications. The IBC highlighted that serious concerns are raised, "if the editing of the human genome should be applied to the germline and therefore introduce heritable modifications, which would be transmitted to future generations."[35]

44. Likewise, the Council of Europe's Convention on Human Rights and Biomedicine (1997) stated in Article 13 that :

> "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."

In addition, the 2001 European Union Directive on Clinical Trials prohibits any gene therapy trial that results in modifications to the subject's germline genetic identity.

**International Debate on Clinical Application of MGRT**

45. In February 2015, following extensive public and parliamentary debate, the UK Parliament voted overwhelmingly in favour of regulations that would enable mitochondrial replacement techniques to be used in clinical practice in the UK. Although the UK Government accepted that these techniques result in germline modification — in that the donated mtDNA will be passed down the maternal (female) line to future generations, it was of the view that these techniques did not constitute genetic modification,[36] which it considered to be the key contention with germline modification. It argued that "these techniques only replace, rather than alter, a small number of unhealthy genes in the 'battery pack' of the cells with healthy ones" and "do not alter [the] personal characteristics and traits of the [resulting child]".[37] As there was no universally agreed definition of "genetic

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33 UNESCO. *Universal Declaration on the Human Genome and Human Rights.* 1997. Article 24.

34 UNESCO. *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention*. 2003. Paragraph 84.

35 UNESCO. *Report of the IBC on Updating its Reflection on the Human Genome and Human Rights*. 2015. Paragraph 104.

36 Department of Health, UK. *Mitochondrial Donation : Government Response to the Consultation on Draft Regulations to Permit the Use of New Treatment Techniques to Prevent the Transmission of a Serious Mitochondrial Disease from Mother to Child*. 2014. See p15.

37 *Ibid.*

modification", the UK Government adopted a "*working* definition… [that] genetic modification involves the germline modification of nuclear DNA (in the chromosomes) that can be passed on to future generations".[38]

46. With the passage of the 2015 Human Fertilisation and Embryology (Mitochondrial Donation) Regulations, the clinical application of MST and PNT has been legalised in the UK, but is subject to licensing control by the Human Fertilisation and Embryology Authority (HFEA). Clinics wishing to perform these techniques are required to adhere to a two-stage licensing process. Besides applying for a licence to carry out MST and / or PNT, clinics must obtain a second authorisation on a case-by-case basis to administer the treatment to particular patients. On 16 March 2017, HFEA approved the first treatment licence for Newcastle Fertility Centre for the clinical application of PNT.[39] In February 2018, it was reported that HFEA granted the first patient licences to two women, both genetic carriers of a mitochondrial disease known as MERRF syndrome, to receive mitochondrial replacement therapy at that Newcastle clinic.[40]

47. Similarly, the US had also considered if the clinical application of mitochondrial replacement techniques should be permitted. Following an application from Dr Shoukhrat Mitalipov to begin clinical trials of MST in humans, the Food and Drug Administration (FDA) held a two-day public hearing in February 2014 to discuss scientific, technological and clinical matters relating to mitochondrial manipulation technologies to prevent the transmission of mitochondrial disease. The FDA advisory committee concluded that more data was needed before trials could be conducted in humans. The committee acknowledged there were serious social and ethical concerns that needed to be addressed, but the FDA was not the appropriate body to do so. As such, an expert committee was set up by Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine to examine the ethical and social policy considerations of novel techniques for the prevention of maternal transmission of mitochondrial DNA diseases.

48. In a report released in February 2016, the committee concluded that clinical investigations of MGRT in humans are ethically permissible, so long as certain conditions and principles are satisfied.[41] Some of the safeguards recommended to the FDA, which will ultimately regulate the use of MGRT in clinical practice, were :

    (i) Consider clinical investigations only if and when initial safety and likelihood of efficacy are established;

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38 Department of Health, UK. *Mitochondrial Donation : Government Response to the Consultation on Draft Regulations to Permit the Use of New Treatment Techniques to Prevent the Transmission of a Serious Mitochondrial Disease from Mother to Child*. 2014. See p15.

39 HFEA, UK. "HFEA statement on mitochondrial donation". Press Release,16 March 2017; and Newcastle University. "Newcastle awarded world's first mitochondrial licence". Press Release, 16 March 2017.

40 Sample I. "UK doctors select first women to have 'three-person babies'". *The Guardian*. 1 February 2018. https://www.theguardian.com/science/2018/feb/01/permission-given-to-create-britains-first-three-person-babies (Accessed March 26, 2018)

41 National Academy of Medicine Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, USA. *Mitochondrial Replacement Techniques : Ethical, Social, and Policy Considerations*. 2016.

(ii) Limit initial clinical investigations to women who are at risk of transmitting a severe mitochondrial genetic disease that could lead to a child's early death or substantial impairment;

(iii) Consider the impact that pregnancy would have on the health of the gestational carrier;

(iv) Allow the implantation of only male embryos created by MGRT in initial clinical investigations and extending later investigations to include female embryos only when safety and efficacy in the male cohorts has been clearly established;

(v) Review the matching of mtDNA subtype of the donor with that of the intended mother, and if compelling, consider such matching as a means of mitigating the possible risk arising from incompatibility of the donor's mtDNA with the nuclear DNA of the prospective mother; and

(vi) Ensure the collection of long-term information regarding the psychological and social effects on children born using MGRT, including their perceptions about identity, ancestry and kinship.

In August 2017, the FDA made clear that any clinical research of MGRT in humans remains prohibited in the US.[42]

49. The Swedish Council of Medical Ethics has also deliberated on techniques of mitochondrial replacement. In 2013 it found such techniques to be ethically unacceptable at the time due to uncertainty concerning the safety and efficacy of these techniques.[43] A majority of the Council members did, however, think that the techniques would be ethically acceptable if they could be done safely with acceptable short- and long-term risks. They were of the view that scientific developments in this area should be followed, and a broad public debate should be carried out before allowing such interventions.

50. The UNESCO IBC has expressed a similar opinion in its 2015 report "*Updating its Reflection on the Human Genome and Human Rights*". The IBC stated that mitochondrial replacement techniques should be "adequately proven to be acceptably safe and effective as treatments" by the international scientific community before being considered for application in humans.[44]

51. In the light of the recent scientific developments and international debate, the BAC considers it important and timely to review the permissibility of germline modification techniques for the prevention of mitochondrial disorders. The next chapter outlines some of the arguments for and against the clinical application of MGRT.

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42 Food and Drug Administration, US. *Advisory on Legal Restrictions on the Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells intended for Transfer into a Human Recipient.* 4 August 2017. https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm570185.htm (Accessed January 25, 2018)

43 The Swedish National Council on Medical Ethics, Sweden. *Summary : Mitochondria Replacement in Cases of Serious Diseases — Ethical Aspects*. 2013. See p5.

44 UNESCO. *Report of the IBC on Updating its Reflection on the Human Genome and Human Rights.* 2015. Paragraph 118.

## CHAPTER 3 : ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

### Possible Benefits of MGRT

### Q1. Why is MGRT being considered? What are the possible benefits of MGRT?

52. The key benefit of MGRT is the potential elimination of mitochondrial disorders caused by mtDNA mutation in the immediate generations, and the avoidance of physical, psychological or social suffering associated with the disorders.[45] As mentioned in Chapter 1, mitochondrial disorders vary widely in symptoms and severity, and could be potentially life-threatening, debilitating or disabling. There is currently no cure for mitochondrial disorders. Women with abnormal mtDNA who wish to be mothers are subject to a great amount of stress and anxiety, as it is difficult to predict whether and to what extent a child born to them would be affected by mitochondrial disorders. MGRT offers an opportunity to mitigate the undesirable outcomes of the "genetic lottery", so that affected individuals could have children potentially unaffected by mitochondrial disorders. This prevents suffering not only for their future children, but also for the prospective parents. Also, compared to children who are limited by disability or ill health due to mitochondrial disorders, healthy children would have, in general, a more "open" future as they have more options available in life.

53. MGRT is more than just a method for persons with abnormal mtDNA to have children who are free from mitochondrial disease — for some it is their only opportunity to have healthy *genetically-related* children. Although existing alternatives such as adoption or IVF using donated eggs allow women with abnormal mtDNA to have children free from mitochondrial disorders, these children are unlikely to be genetically related to them. Even if a sister or a maternal female relative donates her eggs for IVF, the resulting child would not have inherited the nuclear genome from the prospective mother, and hence may not be perceived as "her own". Thus, it could be said that the main benefit of MGRT is the fulfilment of such individuals' deep desire to have genetically-related children.

### Reproductive Autonomy

### Q2. Why is the option to have genetically-related children important?

54. The distinctive benefit of MGRT is that the resulting offspring will be the prospective parents' "own child". This raises the question of why the option to have genetically-related children is so important, as it is the premise underlying the desire for MGRT.

55. It may be argued that the significance of having genetically-related children stems from personal autonomy. Choosing to have one's own child through the use of MGRT — rather than adopting someone else's child or using donated egg — is an exercise of one's reproductive autonomy, and the principle of respect for

[45] MGRT does not exclude future generations from the possibility of developing new mtDNA mutations. mtDNA is known to be more prone to developing mutations than nuclear DNA as DNA repair in the mitochondria is not as robust as that in the nucleus.

persons warrants respect for their reproductive decisions. Hence, MGRT should be permitted because the decision to use it falls within the sphere of reproductive autonomy, which others should respect and support.

56. Indeed, the introduction of IVF and the acceptance of then-unknown risks was also motivated by the desire to allow infertile couples the ability to have their own genetically-related children and for infertile women to experience pregnancy and childbirth. This indirectly reflects the value that society recognises in the desire to have one's genetically-related children.

**Fairness**

**Q3. Will it be unfair not to offer women affected by mitochondrial disorders who want to have genetically-related children access to new technology that would give them the potential to have healthy children of their own?**

57. Another reason why MGRT should be allowed is to ensure fair access to technology. It may be argued that since the technology is available for those suffering from mitochondrial disorders to have a chance at having healthy children of their own, there is a moral imperative arising from the concept of fairness to allow its use by those who require it. Access to MGRT offers women affected by mitochondrial disorders a similar opportunity as other infertile women to have healthy genetically-related children of their own. Since infertile couples are not denied access to IVF, it follows by the principle of fairness that women affected by mitochondrial disorders should not be denied access to MGRT that would give them the potential of the same outcome.

**Welfare of Future Generations**

**Q4. What are your views on the welfare of future generations in the context of clinical trials involving MGRT? Whose welfare should be given precedence — future generations or existing individuals?**

58. As mentioned earlier, one of the BAC's guiding principles is sustainability — that is, any research should not jeopardise or prejudice the welfare of future generations. The unique characteristic of MGRT is its potentially long-lasting impact, affecting not just the resulting children born from these techniques; but, when the resulting child is female, later generations as well. As germline modification will alter the genome of all the cells in the resulting child, including his / her gametes, this modification may be transmitted to subsequent generations through the germline. The welfare of future generations is therefore a key ethical concern of germline modification technology.

59. Genetic-relatedness, if accepted to be the distinctive benefit of MGRT, would apply not only to women affected by mitochondrial disorders, but would extend also to the children born using MGRT. It may therefore be argued that prohibiting the clinical application of MGRT would be denying the prospective child the benefit of a substantial genetic relationship with his / her parents, while avoiding the risk of mitochondrial disease. This argument stems from the principle of beneficence / non-maleficence (or "do no harm"), with a strong focus on possible benefits that the clinical application of MGRT could have for future generations.

60. On the other hand, it could also be argued using the same principle of beneficence / non-maleficence that allowing the clinical application of MGRT could jeopardise the welfare of future generations because of the uncertain risks involved and the potentially trans-generational impact of untested germline modification techniques. This view focuses on the possible harm that could arise from the clinical use of MGRT, which are explored further in the next section.

61. Even on the latter view, a further question arises : does the welfare of future generations take precedence over the welfare, and in particular reproductive autonomy, of the prospective parents? Clinical trials of germline modification techniques are distinctive in that they do not involve just one category of research subjects, but several. It may be argued that rather than the prospective parents who will undergo the procedures, the prospective child of the MGRT should be the foremost concern because he / she would not be in a position to accept the risks imposed by the experimental procedures. While the law prescribes an overriding welfare standard for a child in being, it is not clear what standard applies to future children that result from experimental or risk-laden reproductive technologies like MGRT. There is clearly a duty of reasonable care owed to future children to prevent foreseeable injury, even if the negligence was pre-conception. Such a claim is, however, enforceable only if the child is born alive and suffers the injury.[46]

62. In addition, commentators argue that there is also a moral duty to use the safest procreative method available in order to prevent avoidable harm or suffering, all else being equal.[47] While there is certainly a moral obligation to protect the welfare interests of the future child, this has to be balanced against the legitimate reproductive autonomy interests of prospective parents. Where the technology offers new hope to a woman with mitochondrial disorder who would otherwise not have a healthy child of her own, this adds moral weight to her interest when compared to a situation where alternative reproductive methods, which are safer, exist to achieve the same outcome. It may also be argued that experimental reproductive technologies should not be used where there is a serious risk of harm to the future child, such that it would have been better for that future child if he / she had not been born.[48]

63. In a similar vein, the European Society of Human Reproduction and Embryology Task Force considered that "the interests of future offspring should prevail over the development and progress of science", where the possible harm to the people involved (including the future child) should be outweighed by the possible benefits.[49] Apart from the prospective parents and immediate future child, future

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46 Supreme Court, United States. Missouri : Lough v. Rolla Women's Clinic, Inc. [1993]866 SW 2d 851; NSWCA, Australia. X v Pal (1991) 23 NSWLR 26. Such claims are also recognised in the UK under the Congenital Disabilities (Civil Liabilities) Act 1976.

47 Brock DW. The Non-Identity Problem and Genetic Harms — The Case of Wrongful Handicaps. *Bioethics.* 9 (1995) : 269–75.

48 Peters PG. *How Safe is Safe Enough? Obligations to Children of Reproductive Technology*. Oxford University Press, 2004. Chapter 5.

49 Pennings G *et al*. European Society of Human Reproduction and Embryology Task Force on Ethics and Law 13 : the Welfare of the Child in Medically Assisted Reproduction. *Human Reproduction.* 22, no. 10 (2007) : 2585-2588, p2587.

generations through the maternal line will also be affected by the germline modifications and are arguably also relevant research subjects. Their interests are however more remote and harder to assess.

**Possible Harm to Future Generations**

64. Related to the welfare of future generations is the question of what possible harm could arise from the clinical application of MGRT, which is difficult to assess because the first-in-human trials of MGRT have not been conducted yet. Even after extensive pre-clinical studies in animals and human embryos are conducted, the long-term safety, efficacy and effects of any germline modification technique cannot be adequately ascertained until longitudinal studies over several generations of descendants from the use of MGRT have been performed. Nevertheless, there are at least two foreseeable categories of harm to future generations that could arise from the clinical application of MGRT : (1) health or developmental problems, and (2) undesirable psychosocial impact.

**Health or Developmental Problems**

65. As an evaluation of the safety of MGRT is not the main intention of this paper, we will only briefly note two safety issues that have been raised concerning MGRT. Although mitochondria are usually referred to as the "batteries" of the cell, recent research indicates that complex interactions which exist between nuclear DNA and mtDNA may affect many cellular functions. It has therefore been questioned if a mismatch between nuclear and mitochondrial DNA caused by MGRT might result in unexpected adverse effects on the resulting child. Another concern is that manipulation of the eggs or zygotes during MGRT may cause epigenetic changes that may result in developmental or health problems in the resulting child.

66. With regard to the first concern about nuclear-mitochondrial DNA incompatibility, it has been proposed that mtDNA haplogroup matching could be considered when selecting donor eggs. In a 2016 study conducted on mice, researchers reported that mtDNA and nuclear DNA incompatibility resulted in embryonic lethality.[50] However, insofar that the incompatibility was a result of using two mouse strains (interspecies), it is unclear if the findings will be relevant to humans. Based on the MST study involving rhesus macaque monkeys (mentioned above in paragraph 33), there is currently no evidence that incompatibility between the mother's nuclear DNA and the donor's mtDNA will affect the health or development of the resulting child,[51] nor that MGRT will cause epigenetic alterations (if any) with far-reaching health consequences. More recently, a bioinformatics study also discovered that naturally-occurring mismatched nuclear-mitochondrial DNA combinations can co-exist within

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50 Ma H *et al*. Incompatibility between Nuclear and Mitochondrial Genomes Contributes to an Interspecies Reproductive Barrier. *Cell Metabolism.* 24 (2016): 283-294.

51 Tachibana M *et al*. Towards Germline Gene Therapy of Inherited Mitochondrial Diseases. *Nature.* 493 (2013) : 627-631. Two genetically distant sub-populations of rhesus macaque monkeys were used as the nuclear DNA and mtDNA donors, resulting in genetic differences distant enough to "[imitate] haplotype differences between humans".

healthy humans. Thus, the study predicts that it is unlikely that nuclear-mitochondrial DNA incompatibility bears any significant risk for MGRT.[52] Another possible safeguard, which was proposed by the US Institute of Medicine, is to carry out trials of MGRT with only male embryos to remove the risk of transmission of unforeseen defects to subsequent generations.

**Undesirable Psychosocial Impact**

**Q5. What psychological or social impact might MGRT have on children born using such techniques? Is it true that children conceived through MGRT will have "three parents"?**

67. Concerns have been raised that mitochondrial replacement, even if proven to be safe and efficacious, could impose psychosocial harm due to the mixed genetic heritage of the resulting children. It has been suggested that children, if informed that they were born via MGRT and possess genetic material from three different persons, may form a self-conception that is troubling, ambiguous or conflicted. Harm may also arise from confusing relationships with their family members.

68. There is an emerging concept that understanding one's genetic origins is of great importance in one's personal identity, thereby justifying the mandatory disclosure of selective identifying information relating to gamete donors in assisted reproductive treatments in some jurisdictions including the UK, Sweden, Norway and Germany.[53] Available studies of individuals seeking information under the new regulatory provisions granting access to donor information, albeit cross-sectional in nature, indicated motivations of curiosity, a desire to know more about their ancestry, medical history and, therefore, a better understanding of their identity.[54]

69. However, while the disclosure of information pertaining to gamete donors has been mandated in the UK, the same requirement has not been extended to mitochondrial donors.[55] It is argued that in contrast to donors of gametes contributing to the nuclear genome of the resulting child, mitochondrial donors do not convey any physical resemblances or personality characteristics that would form the basis of an identifying or distinguishing link with that donor.[56] Moreover, genetic identity is only one aspect of personal identity; the latter being dependent also on one's upbringing and life experiences.

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52 Rishishwar L & Jordan K. Implications of Human Evolution and Admixture for Mitochondrial Replacement Therapy. *BMC Genomics.* 18 (2017) : 140.

53 UK. *Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004.* It is mandatory in the UK to disclose donor identifying and other information to children conceived from donor gametes in IVF procedures once they turn 18 years of age, should they desire to know. See also : Cohenn G *et al*. Sperm Donor Anonymity and Compensation : an Experiment with American Sperm Donors. *J Law Biosci.* 3, no. 3 (2016) : 468-488.

54 Nuffield Council on Bioethics. *Novel Techniques for Prevention of Mitochondrial Disorders : an Ethical Review.* 2012. Paragraph 4.106.

55 UK *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015* Regulation 11

56 Nuffield Council on Bioethics. *Novel Techniques for the Prevention of Mitochondrial Disorders : an Ethical Review.* 2012. Paragraph 4.112-4.114.

70. As a child born of MGRT will inherit genetic material from three persons, the media has bandied about the notion of the "three-parent child", and some have argued that the feelings of ambiguity of genetic and social roles in such a situation may affect the future child's well-being or self-identity.[57] However, the amount of mtDNA that will be inherited from the donor is very small, compared to the nuclear DNA contribution from the two prospective parents. Moreover, as mtDNA is maternally inherited, a father is unlikely to have the same mtDNA makeup as his child.[58] There is also no indication that having a different genetic makeup (especially if such genetic material does not confer any physically noticeable traits such as in the case of mtDNA) would make a critical difference to the social and experiential upbringing afforded to the child.

71. Perceptions of familial relationships depend on various factors, many of which are subjective and experiential. IVF with donor gametes and adoption are no longer uncommon in Singapore; hence, notions of genetic parents, gestational parents and social parents should no longer be unfamiliar or unacceptable in our community. There is no compelling evidence that the relationship between gamete donors, social parents and resulting children will be confusing; even if there was confusion, much less any evidence for harm to the children.[59]

72. Such psychosocial concerns might also be mitigated by using a maternally-related egg donor, or through haplogroup matching, such that the mitochondrial replacement would involve mtDNA that the child would have inherited if there was no disease-causing mutation in the mother. In Singapore, the law would allay any further confusion about parental status, as the Status of Children (Assisted Reproduction Technology) Act (Cap. 317A) makes clear (on the assumption that the Act applies in the case of MGRT)[60] that the gestational mother is treated as the legal mother, while egg and sperm donors are not treated as parents. Furthermore, appropriate disclosure and explanation of the MGRT to the child, when the child attains sufficient maturity, may mitigate any confusion or negative social reactions that might affect the child's self-identity.

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57 Professor Brenda Almond's submissions to the Nuffield Council on Bioethics in its consultation exercise for their report. In : Nuffield Council on Bioethics. *Novel Techniques for Prevention of Mitochondrial Disorders : an Ethical Review.* 2012. Paragraph 4.64.

58 It is possible, for example in cases where a population is homogenous for a particular haplogroup of mtDNA, that the father so happens to possess the same haplogroup of mtDNA as the mother.

59 Appleby J & Karnein A. "On the moral importance of genetic ties in families". In *Relatedness in Assisted Reproduction : Families, Origins and Identities*. Eds. Tabitha Freeman *et al*. Cambridge University Press, 2014. Chapter 4. p87.

60 Even if the Act does not apply, the definition of "fertilization procedure" in section 2(1) can be expanded by subsidiary legislation to cover MGRT.

## Assessing the Risks and Benefits

### Q6. Do the possible benefits justify first-in-human clinical trials of MGRT?

73. The current challenge lies in determining what an ethically acceptable threshold of risk versus benefits should be, in comparison with the available alternatives, for first-in-human trials to proceed. It has been argued that any child born by medically assisted reproduction should have a reasonable chance of an acceptable quality of life, and the risks should be reduced as much as reasonably possible.[61] Unavoidable risks must be justified by the potential benefits to subjects. In contrast, it may be argued that clinical trials should present a balance of potential benefits and harms comparable to that presented by available alternatives.[62]

74. There is however a difficulty in applying either of these formulations in trials involving MGRT. Although it is the prospective parents who use the new technology, it is the child (and future generations) who will principally be affected, and there is no way to know if the technology is safe until longitudinal studies have been carried out. It has been said that pre-clinical research "can only serve to reduce the risk…but with caveats concerning for whom this type of risk reduction strategy might be suitable and highlighting areas that need close attention".[63] As such, it has been suggested that it would be appropriate to offer MGRT "as a clinical risk reduction treatment for carefully selected patients".[64]

75. What rigour and standard of evidence is required to establish safety? One approach may be to define a maximum threshold of abnormal mtDNA that an embryo can carry, below which any embryo would be deemed safe enough for implantation. However, given the poor correlation between abnormal mtDNA load and manifestation of symptoms,[65] it has been proposed that a "higher-than-threshold" level of risk is acceptable so long as it is a step down from the otherwise high level that would be present by natural reproduction.[66] In other words, it is ethical to proceed so long as the new technique reduces the risk of transmission of mitochondrial disorder. Opponents would, however, argue that it is not ethically acceptable to subject the prospective child to unknown risks of MGRT just in order to satisfy a desire to have a genetically-related child, because there are existing alternatives such as IVF using donated eggs that would as effectively prevent the transmission of mitochondrial disorders without the same level of uncertainty surrounding safety and efficacy. In light of the potentially trans-generational consequences of MGRT, a precautionary approach that requires a higher threshold of confidence regarding pre-clinical evidence of safety and efficacy may be justified.

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61 Bredenoord AL & Braude P. Ethics of Mitochondrial Gene Replacement : from Bench to Bedside. *BMJ.* 341 (2010) : c6021.

62 Dresser R. Designing Babies: Human Research Issues. *IRB: Ethics & Human Research* 26(2004) 1-8

63 HFEA, UK. *Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2016 Update.* November 2016. See p7.

64 *Ibid.*

65 The relationship between abnormal mitochondrial load and manifestation of symptoms was discussed in paragraph 11 above.

66 *Ibid*, p39.

## Slippery Slope

### Q7. Will allowing MGRT create an unethical exception to the prevailing prohibition on altering the human germline?

76. Although MGRT is a type of germline modification as it changes the inherited genome of the resulting child, there are important differences between MGRT and other germline therapies targeting the nuclear genome, which were the focus of past discussions. In MGRT, only the mitochondrial genome is replaced while the nuclear genome remains unchanged. Since the mitochondrial genome comprises much fewer genes, the scope of functional changes that MGRT could introduce is relatively limited. Another difference is that the resulting modification is only transmissible through the maternal line. It is therefore theoretically possible to prevent any inter-generational impact of MGRT by only selecting for male offspring. Lastly, MGRT does not entail genome editing, but rather a replacement of whole intact mitochondria. MGRT will not create any "novel" mtDNA sequences that do not already exist naturally, hence implying low safety risks.

77. Despite these differences, some opponents of MGRT are nevertheless concerned that permitting these techniques would be a step down the "slippery slope" towards nuclear germline modification, and towards enhancement for "designer babies". There are two distinct senses of the slippery slope objection. The first is technical in nature — that once the use of these technologies becomes legitimate, it would thereby open the doors to other less safe or less established practices using these same techniques. For example, researchers from Ukraine have claimed the use of PNT for infertility.[67] As the two women on whom the technique was carried out had previous failed IVF cycles because of embryo arrest, PNT was used to provide a "potentially healthier cellular machinery around" the pronuclei to overcome embryo arrest. The Ukrainian researchers have been criticised for using PNT to overcome infertility (vis-à-vis to prevent a hereditary disease) when evidence of safety is still lacking. There is also no evidence that defective mitochondria were the reason for embryo arrest since there are other components in the cytoplasm that could have contributed to the women's infertility.

78. The second sense of a slippery slope is more conceptual. By taking this first step in allowing a form of germline modification, it may become harder to argue against more morally contentious forms of germline modification in the future. For instance, there are many genes in the nuclear genome that are essential in mitochondrial processes of energy production. If the replacement of abnormal mitochondria is allowed on the basis that there is a moral imperative to assist patients / carriers of mitochondrial disorders to have healthy genetically-related children, then the argument follows that editing of the nuclear genome for the same purpose should also be allowed, if the new technology is shown to be safe. Thus, mitochondrial replacement could be viewed as the thin edge of the wedge towards heritable nuclear germline manipulation.

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[67] Coghlan A. "Exclusive : '3-parent' baby method already used for infertility". *New Scientist.* 10 October 2016. https://www.newscientist.com/article/2108549-exclusive-3-parent-baby-method-already-used-for-infertility/ (Accessed March 26, 2018)

79. The slippery slope is an important argument, particularly in Singapore, where there are currently no explicit legal prohibitions on nuclear germline modification, apart from the BAC's recommendation for an ethical moratorium on clinical applications of such technology. However, since any research involving the use of human eggs or human embryos[68] and any new assisted reproductive service[69] require special approval from the Director of Medical Services, the objection could be addressed by enhancing current regulation to limit the use of MGRT to the prevention of serious mitochondrial disease; an approach adopted similarly in the UK. A clear regulatory line could also be drawn based on the material distinction between the mitochondrial genome, which mainly codes for energy production; and the nuclear genome, which is responsible for all bodily functions.

**Distinction between Different MGRT Techniques**

**Q8. Is there any ethical difference between PNT, MST and PBT (PB1T and PB2T)? Assuming that all are equally safe and effective, is one technique more acceptable than the other?**

80. The UK Parliament had taken the position that both MST and PNT should be permitted, as it did not consider one technique to be preferable to the other at that point in time.[70] While that decision was made in early 2015, more recent papers have not conclusively shown either MST or PNT to be preferable to the other on the basis of safety or efficacy. Having taken into account these studies, the HFEA, in its 2016 scientific review, reaffirmed that both PNT and MST "were sufficiently safe to proceed cautiously and in restricted circumstances".[71]

81. However, the embryo is usually regarded as having a higher moral status than the egg. As such, MST may be perceived as more ethically acceptable than PNT because MST involves manipulation of the egg whereas PNT is a form of embryo modification. On the other hand, it has been suggested that while PNT is a form of pre-emptive treatment – since mitochondrial replacement is carried out on an unhealthy embryo, MST is a form of selective reproduction involving egg manipulation.[72] On the grounds of eugenics, MST is therefore the less ethically acceptable option than PNT.

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68 Any human biomedical research involving the use of human eggs or human embryos falls under the category of "Restricted Human Biomedical Research" of the *Human Biomedical Research Act 2015*, Section 31 and Fourth Schedule.

69 Ministry of Health, Singapore. Licensing Terms and Conditions on Assisted Reproduction Services. April 2011. Paragraph 5.47.

70 HFEA, UK. *The Third Scientific Review of Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception.* 2014. See p5.

71 HFEA, UK. *Scientific Review of Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception : 2016 Update*. November 2016. Paragraph 6.1.

72 Wrigley A *et al.* "Mitochondrial Replacement : Ethics and Identity", *Bioethics* (2015) 29 : 631-638. Wrigley argues that if we take the Origin view (also known as gametic essentialism) of identity, the numerical identity of a person is dependent on the fertilisation of one particular egg by one particular sperm. The resulting embryo would be a numerically different person than if that particular egg had been fertilised by another sperm instead. This is also known as the non-identity claim. In MST, the

82. Polar bodies are usually described as the "by-products" of oogenesis because they do not become fertilised or developed further, but degenerate instead. Is it ethically contentious that PBT would result in the conception of a life that would not have come into existence otherwise? In addition, PBT may also be used concurrently with MST and / or PNT to create multiple embryos from the prospective mother's egg (and two donor eggs). Wang *et al*. successfully performed the techniques concurrently in mouse eggs, providing in-principle proof that it could be done.[73] Combined use of MGRT would therefore allow for the more efficient usage of the mother's eggs, as it increases the chances of creating a successful embryo with low abnormal mtDNA carryover for every egg retrieved from the prospective mother. Moreover, these embryos would not be genetically identical to each other (i.e. this would not be a form of reproductive cloning) as the nuclear material contained in polar bodies are the complementary set of that carried in the egg. Is it ethically acceptable to combine the use of PBT with MST and / or PNT to generate more embryos, or possibly sibling embryos, using just one egg from the prospective mother?

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## Invitation to Comment

Before making any recommendations on MGRT, the BAC would like to seek public views on whether the clinical application of MGRT should, or should not, be permitted in Singapore. The BAC values feedback from all interested individuals and organisations. Interested parties can specifically address the issues and questions raised in this consultation paper, or comment on any other aspects of MGRT.

Please send your responses and comments, together with a completed respondent's form (*next page*) :

- via email to : bioethics_singapore@moh.gov.sg
- via post to : Bioethics Advisory Committee Secretariat
  1 Maritime Square
  #09-66 HarbourFront Centre
  Singapore 099253

The closing date for responses is **15 June 2018**.

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sperm that would have fertilised the egg if MST had been performed on would practically never be the same sperm that would have fertilised the egg if MST had not been performed. The embryo that would have been created after MST is a numerically different person than if MST had not been performed. Therefore, MST should be viewed as a form of selective reproduction, as one is essentially selecting a healthier egg to be used in creating an embryo. However, the same does not apply for PNT. Therefore, PNT should be perceived as a "treatment" as the numerical identity of the embryo does not change.

[73] Wang T *et al.* Polar Body Genome Transfer for Preventing the Transmission of Inherited Mitochondrial Diseases. *Cell*. 157 (2014) : 1591-1604.

BIOETHICS ADVISORY COMMITTEE SINGAPORE

# Respondent's Form to the Bioethics Advisory Committee's Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology"

Please complete this form and send it together with your responses and comments, to the BAC Secretariat, by 15 June 2018 :

- via email : bioethics_singapore@moh.gov.sg; or
- via post : 1 Maritime Square, #09-66 HarbourFront Centre, S(099253)

**Name :** _____

**Email Address :** _____

**Are you responding in your personal capacity or on behalf of your organisation?**

☐ Personal ☐ Organisation : _____

**May we include your / your organisation's response in the final report?**

☐ Yes, publish my / my organisation's response

☐ Yes, but anonymously

☐ No, do not publish my / my organisation's response

**Would you like to receive a copy of the final report when it is published?**

☐ Yes, send a digital copy to :

- ☐ the email address indicated above
- ☐ the following email address(es) : _____

☐ Yes, send a printed copy to the following mailing address(es) :

_____

☐ No, but notify me / my organisation of the publication at :

- ☐ the email address indicated above
- ☐ the following email address(es) : _____

☐ No, and I / we do not wish to be notified of the publication.

**Please let us know how you got to know about the consultation :**

☐ Received notification by email

☐ BAC's website

☐ Newspapers : _____

☐ Others : _____

***Thank you for taking the time to respond to our consultation.***

## GLOSSARY

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|---|---|
| **Adenosine triphosphate (ATP)** | A compound that contains a large amount of stored chemical energy in its phosphoanhydride bonds. The breakdown of ATP (three bonds) into adenosine diphosphate (ADP, two bonds) releases energy that is used for metabolic processes and other cellular functions. |
| **Allele** | A variant form of a gene. Humans (and other diploid organisms) have two alleles, one on each chromosome inherited from a parent. |
| **Amniocentesis** | A prenatal test in which a small amount of amniotic fluid is removed from the amniotic sac using a needle inserted into the uterus through the abdomen, to screen for genetic abnormalities in the developing foetus. The test is usually carried out from 14 weeks of pregnancy onwards. |
| **Autosomal recessive** | An observable feature that develops only when two copies of the same allele are present. |
| **Cardiomyopathy** | A decrease of the heart muscle which can be inherited. It can cause heart failure, which is potentially fatal. |
| **Chorionic villus sampling** | A prenatal test in which a sample of chorionic villus is removed from the placenta, either through the cervix or the abdomen, to screen for genetic abnormalities in the developing foetus. The test is usually carried out between the 10th and 12th week of pregnancy. |
| **Chromosome** | A thread-like structure in the cell that is comprised of a single molecule of tightly coiled deoxyribonucleic acid (DNA) bound to proteins called histones. The DNA molecule contains genes in a linear sequence. |
| **Deoxyribonucleic acid (DNA)** | The hereditary material that carries genetic information in humans and almost all other organisms. It is a macromolecule comprised of two nucleotide strands twisted around each other in a ladder-like (or "double helix") arrangement. There are four types of nucleotides – adenine which pairs with thymine, and cytosine with guanine. |
| **Embryo** | The earliest stage of development of an organism, from the time of fertilisation up to eight weeks post-fertilisation. |
| **Encephalopathy** | A disease that damages the brain. |
| **Endocrine** | Relating to glands that secrete hormones directly into the blood. The endocrine system regulates bodily functions including metabolism, growth and development, sleep and mood. |
| **Enzyme complex** | The intermediate formed when a substrate molecule interacts with the active site of an enzyme. Following the formation of an enzyme–substrate complex, the substrate molecule undergoes a chemical reaction and is converted into a new product. |

## GLOSSARY

| | |
|---|---|
| **Epigenetics** | The study of heritable changes in gene expression that are caused by factors such as DNA methylation without a change in the DNA sequence itself. |
| **Foetus** | The stage of development of an organism beyond the embryo (more than eight weeks post-fertilisation) and before birth. |
| **Gamete** | A reproductive cell (sperm or egg) which contains half the chromosome complement of a somatic cell. Uniting two gametes restores the full complement. |
| **Gene** | A region of the DNA that encodes for a trait (an observable feature); the basic unit of heredity. |
| **Gene pool** | The stock of all the different alleles in a population. |
| **Genome** | The complete set of genetic material in a cell or an organism. |
| **Germline** | The lineage of germ cells from which eggs and sperm are derived. |
| **Haploid** | Possessing only one set of unpaired chromosomes. |
| **Haplogroup** | A group of similar and closely related haplotypes. |
| **Haplotype** | A set of alleles of closely linked genes on a single chromosome that are often inherited together. |
| **Heteroplasmy** | Having two or more mitochondrial DNA variants within a person, cell, or mitochondrion. |
| **Homoplasmy** | Having a single uniform set of mitochondrial DNA within a person, cell, or mitochondrion. |
| **MERRF syndrome** | MERRF, or Myoclonic Epilepsy with Ragged Red Fibers, is a mitochondrial disorder caused by mutation of a person's mtDNA. It is characterised by muscle twitches (myoclonus), weakness (myopathy) and progressive stiffness (spasticity). The muscle cells of affected individuals appear abnormal when stained and viewed under the microscope, and show up as "ragged-red fibers". |
| **mtDNA carryover rate** | The amount of abnormal mtDNA carried over from the prospective mother into the embryo after MGRT. |
| **Nucleus** | A membrane-enclosed organelle of the cell that carries most of the cell's genetic material. |
| **Oocyte** | An egg cell. |
| **Prenatal** | During pregnancy and before birth. |
| **Spermatocyte** | A maturing sperm cell. |
| **Spindle-chromosome complex** | A complex found within an egg's nucleus which consists of the maternal chromosomes held together by a protein scaffold. |
| **Zygote** | The diploid cell resulting from the fusion of a sperm and an oocyte; a fertilized egg. |

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## Policies on Clinical Application of Human Germline Modification

| Jurisdiction | Regulatory Position | Relevant Law or Guideline |
|---|---|---|
| Australia | Ban | **Prohibition of Human Cloning for Reproduction and Regulation of Human Embryo Research Amendment Act (2006)**<br>It is an offence to import, export or place a prohibited embryo in the body of a woman (section 20), where a prohibited embryo refers to :<br>(f) a human embryo that contains a human cell...whose genome has been altered in such a way that the alteration is heritable by human descendants of the human whose cell was altered... |
| Canada | Ban | **Assisted Human Reproduction Act (2004)**<br>Altering the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants is a prohibited procedure (section 5(1)(f)). |
| China | 'Soft' Ban * | **Guidelines on Human Assisted Reproductive Technologies (2003)**<br>Genetic manipulation of human gametes, zygotes or embryos for the purpose of reproduction is prohibited. |
| Finland | Ban | **Medical Research Act (488/1999, 295/2004, 794/2010)**<br>Research on embryos and gametes for the purpose of developing procedures for modifying hereditary properties is prohibited, unless the research is for the purpose of curing or preventing a serious hereditary disease (section 15). However, embryos that have been used for research may not be implanted in a human body (section 13), where research refers to an intervention in the integrity of a person, human embryo or human foetus for the purpose of increasing knowledge... (section 2 (1)) |
| Germany | Ban | **Embryo Protection Act (1990)**<br>Artificially altering the genetic information of a human germ cell, and using a human germ cell with artificially altered genetic information for fertilisation, are prohibited (section 5). |

## Policies on Clinical Application of Human Germline Modification

| Jurisdiction | Regulatory Position | Relevant Law or Guideline |
|---|---|---|
| India | 'Soft' Ban * | **National Bioethics Committee, Ethical Policies on the Human Genome, Genetic Research & Services (2002)**<br>Germline therapy in humans shall be proscribed, due to the present state of knowledge of the field.<br>**Indian Council of Medical Research, Ethical Guidelines for Biomedical Research on Human Participants (2006)**<br>Germline therapy is prohibited (p70). |
| Israel | Permissible under certain conditions | **Law on the Prohibition of Genetic Intervention Act (Human Cloning and Genetic Manipulation of Reproductive Cells), (1999, renewed 2004, 2009, 2016 and valid until May 23, 2020)**<br>Using reproductive cells that have undergone a permanent intentional genetic modification (Germ Line Gene Therapy) in order to cause the creation of a person is prohibited (section 3(2)). However, the Minister has the power to permit through regulations the performance of specific kinds of genetic interventions that are prohibited under s3(2), "if he is of the opinion that human dignity will not be prejudiced, upon the recommendation of the advisory committee and upon such conditions as he may prescribe" (section 5(a)).<br>It is unclear if the reproductive use of *embryos* that have undergone genetic modification is prohibited. |
| Italy | Permissible under certain conditions | **Rules on Medically Assisted Procreation, Law 40/2004**<br>Any form of eugenic selection of gametes or embryos, and interventions that, through breeding techniques, handling or otherwise using artificial processes, are intended to alter the genetic heritage of the embryo or gamete or to predetermine genetic characteristics, are prohibited, *except when it is for diagnostic and therapeutic purposes, as set out in paragraph 2* (Article 13(3b)). Paragraph 2 states that the clinical and experimental research on human embryo is permitted provided its aim is for diagnostic and therapeutic purposes *which are exclusively associated with the protection of the health and development of the embryo itself, and if no alternative methodologies are available.* |

## Policies on Clinical Application of Human Germline Modification

| Jurisdiction | Regulatory Position | Relevant Law or Guideline |
|---|---|---|
| Japan | Ban | **Guidelines of Clinical Research Regarding Gene Therapy (2015)**<br>Clinical research that intentionally conducts or may conduct genetic modification of human germ cells or embryos is prohibited. (Article 7) |
| Malaysia | 'Soft' Ban * | **Guideline of Malaysian Medical Council on Assisted Reproduction (MMC Guideline 003/2006)**<br>Under no circumstances should the genetic structure of any cell be altered while it forms part of an embryo (p16) |
| New Zealand | Ban | **Human Assisted Reproductive Technology Act (2004)**<br>Implanting into a human being a genetically modified gamete, human embryo, or hybrid embryo is prohibited (Schedule 1 : Prohibited Actions). |
| Norway | Ban | **Biotechnology Act (2003/100)**<br>Gene therapy on foetuses and embryos and gene therapy that may involve genetic modification of germ cells is prohibited (§ 6.2) |
| South Korea | Ban | **Bioethics and Safety Act (Revised 2014)**<br>Gene therapy on sperm, oocytes, embryos or foetuses is prohibited (Article 47(2)). |
| Sweden | Ban | **Genetic Integrity Act (2006)**<br>Experiments for the purposes of research or treatment that entail genetic changes that can be inherited in humans (section 3), and treatment methods that are intended to bring about genetic changes that can be inherited in humans (section 4), are prohibited. |
| Thailand | Permissible | There are no explicit prohibitions against the clinical application of human germline modification.<br>The creation of a human being with the usage of other procedures than the fertilisation of sperm and egg (Section 38) is prohibited in the Act Providing Protection for Children Born Through Assisted Reproductive Technologies (B.E 2558 / 2015). However, it is unclear if this prohibition applies to human germline modification techniques in which the embryos were created by the fertilisation of sperm and egg. |

## Policies on Clinical Application of Human Germline Modification

| Jurisdiction | Regulatory Position | Relevant Law or Guideline |
|---|---|---|
| United Kingdom | Nuclear Genome Editing – Ban<br><br>Mitochondria Replacement – Permissible under certain conditions | **Human Fertilisation and Embryology Act (1990, amended 2008)**<br>It is prohibited to place in a woman gametes or embryos that have altered nuclear DNA (Section 3).<br><br>**Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015**<br>MST and PNT are the only allowed techniques for mitochondrial donation (Regulations 4 and 7). No genetic modification is to be done to the resulting egg or embryo (Regulations 3(c) and 6(c)). In addition, Regulation 9 ensures that existing treatment licences do not enable the use of eggs embryos and any new licence will require express provision to enable such eggs or embryos. |
| USA | Nuclear Genome Editing – 'Soft' Ban *<br><br>MGRT Research – Ban | **Consolidated Appropriations Act, 2017**<br>Stat. 173. Sec. 736. prohibits the US Food and Drug Administration (FDA) from considering applications for "an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is intentionally created or modified to include a heritable genetic modification."<br><br>**Federal Notice on "Final Action Under NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules" (March 2016)**<br>The NIH will not at present entertain proposals for germ line alterations. (p15320)<br><br>**Advisory on Legal Restrictions on Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells Intended for Transfer into Human Recipient (August 2017)**<br>The FDA explicitly prohibits any clinical research that involves using MGRT in humans. |

* 'Soft' Ban = prohibited / restricted under guidelines or other non-legislative measure