Mitochondrial Genome Replacement Technology

An Interim Report By

The Bioethics Advisory Committee

Singapore

2021

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The Bioethics Advisory Committee, Singapore 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. The Bioethics Advisory Committee, Singapore studies emerging areas in human biomedical research, 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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FOREWORD

Our identification and understanding of mitochondrial diseases have come a long way since they were first described by a group of Swedish investigators in 1962. The advent of molecular medicine, especially DNA sequencing and gene modification techniques, has significantly changed how we view this group of rare, hereditary and frequently debilitating diseases.

Until recently, it appeared that there was no certain way to prevent transmission of mitochondrial diseases from carrier mothers who wished to have genetically related children. However, recent international developments and advances in biomedical science now offer affected families the possibility of preventing the birth of children with inherited mitochondrial diseases. In light of intense global interest in Mitochondrial Genome Replacement Technology (MGRT), the Bioethics Advisory Committee (BAC) embarked on an in-depth survey of the state of the art, regulatory policies in other jurisdictions, consensus views of professional bodies, and closely monitored instances when these techniques were performed. This interim report presents the BAC's position on whether clinical application of mitochondrial genome replacement techniques should be permitted in Singapore.

As an independent advisory body to the Singapore Government, the BAC has a duty to balance the promise of MGRT in preventing the inter-generational transfer of mitochondrial disorders with the protection of individuals and societal values. In doing so, the BAC is minded that this consideration must take into account the ongoing advances of biomedical science and its relationship with the interests of Singapore and Singaporeans, as well as the overarching potential impact on humanity as a whole.

The BAC expresses its gratitude to all community representatives and individuals who provided their views at the various consultation platforms. The BAC considers itself privileged to have witnessed the passionate participation by all involved in this process, and believes that the development of a perspective in the context of our multi-racial and multi-religious society is predicated on the willingness of her people to engage in open, well-informed and frank discussions of significant contemporary developments. This Singaporean perspective, appropriate to our society and values is crucial for Singapore's continued relevance in shaping biomedical ethics on the global stage.

The BAC will continue to monitor developments and revisit the issue when further scientific evidence and clinical experience become available. We remain optimistic that in time to come, affected carriers who have a strong desire for healthy genetically related children will be able to do so reliably and safely.

Chief District Judge (Ret.) Richard Magnus
Chair
Bioethics Advisory Committee

I. Background to the Interim Report

1. In 2014, the Bioethics Advisory Committee (BAC) formed the Mitochondrial Genome Replacement Technology (MGRT) Review Group comprising local and international experts for the purpose of reviewing the BAC's position on germline modification, with a focus on MGRT.[i]

2. This was followed by the release of a consultation paper on 19 April 2018 titled 'Ethical, Legal and Social Issues Arising From Mitochondrial Genome Replacement Technology' (MGRT consultation paper–Annexe A).[ii] The BAC also conducted public consultations from 20 April 2018 to 15 June 2018 to seek public feedback on the potential issues related to the clinical application of this emerging technology in humans.

3. This interim report supplements the topics discussed in the MGRT consultation paper, and sets out the BAC's interim position, given the current state of MGRT research and public feedback.

II. Overview of the Content Covered in the MGRT Consultation Paper

4. Chapter 1 of the consultation paper summarised concepts in genetics and current alternatives for women carrying abnormal mitochondrial DNA (mtDNA) to raise healthy children, such as adoption, *in vitro* fertilisation (IVF) using healthy donor eggs, preimplantation genetic diagnosis (PGD), and prenatal diagnosis (PND).

5. Additionally, the following observations were made:
   (i) The prevalence of heritable mitochondrial disorders in Singapore has not been studied, and is therefore unknown.
   (ii) There is currently no cure for mitochondrial disorders, although interventions to reduce the severity of symptoms are available for some.

6. In Chapter 2, an explanation of germline modification and an overview of MGRT techniques and international developments were provided. Techniques outlined included Maternal Spindle Transfer (MST), Pronuclear Transfer (PNT), and Polar Body Transfer (PBT).

7. In Chapter 3, ethical, legal and social issues arising from MGRT were discussed.

8. This interim report is intended to be read in conjunction with the consultation paper, and will not traverse ground previously covered. As such, the following sections are meant to supplement the material contained in the consultation paper by summarising developments since April 2018.

III. Feedback Received After Release of the MGRT Consultation Paper

9. Following release of the MGRT consultation paper, dialogue sessions were conducted with Institutional Review Board (IRB) members, clinicians, researchers, religious leaders, and the general public between April and June 2018. During these sessions, questions posed in the consultation paper were discussed:

   (i) What are the possible benefits of MGRT?
   (ii) What are the psychological or social impacts on children born using such techniques?

[i] The composition of the BAC and the Mitochondrial Genome Replacement Technology Review Group can be found in the 20 April 2018 consultation paper (Annexe A).

[ii] BAC. (2018). *Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology: A Consultation Paper*.

(iii) Is it unfair to prevent women who harbour mitochondrial mutations from access to new technology that offers them the potential to have healthy genetically-related children?
(iv) Should the welfare of future generations take precedence over the wishes of existing individuals (i.e. the prospective parents), or *vice versa*?
(v) Assuming that all techniques are equally safe and effective, are there any ethical distinctions to be drawn between the various mitochondrial replacement techniques?

10. The Distribution List of the consultation paper is in Annexe B. All written feedback received by the BAC is in Annexe C. Salient views and concerns expressed at dialogue sessions are addressed in Section VI below.

IV. International and Scientific Developments Since the Release of the MGRT Consultation Paper

United Kingdom

11. The UK legalised the clinical application of MGRT in 2015.[iii] In 2019, a team at Newcastle University developed a statistical model to identify cases in which PGD would likely be unsuccessful, and would therefore be good candidates for MGRT in the UK.[iv] While the number of submitted and accepted applications to the UK's Human Fertilisation & Embryology Authority (HFEA) to undergo MGRT is not available in the public domain,[v] HFEA meeting minutes state that at least 10 patient applications have been approved since the first application was submitted in August 2017.[vi] There have been no reports of pregnancies or live births at the time of writing.

Australia

12. In June 2018, Australia's Senate Community Affairs References Committee released their report following an inquiry into the *Science of Mitochondrial Donation and Related Matters*.[vii] In its report, the Committee noted the 'strong potential of mitochondrial donation to address the debilitating effects of inheriting mitochondrial disease [and recommended that] public consultation be undertaken regarding the introduction of mitochondrial donation to Australian clinical practice'.[viii]

13. The Australian Government has since authorised the National Health and Medical Research Council (NHMRC) to establish a Mitochondrial Donation Expert Working Committee to provide a range of expertise and perspectives on the legal, regulatory, scientific, and ethical issues surrounding mitochondrial donation.[ix] The NHMRC held a public consultation from September to November 2019 to obtain views from the Australian community on the social and ethical issues associated with mitochondrial donation.[x] The NHMRC is expected to submit its advice to the Australian Government in due course.

[iii] Gallagher, J. (2015, Feb 24). UK approves three-person babies. *BBC*. Retrieved from https://www.bbc.com/news/health-31594856 on 2019, Aug 30.
[iv] Pickett, S., et al. (2019). Mitochondrial Donation—Which Women Could Benefit? *New England Journal of Medicine*, *380*(20), 1971-1972. DOI: 10.1056/nejmc1808565.
[v] The HFEA is the UK's independent regulator of fertility treatment and research using human embryos. It approves the provision of MGRT in certain, specific cases.
[vi] HFEA. (n.d.). Authority Meeting Documents. Retrieved from https://www.hfea.gov.uk/about-us/our-people/authority-meetings/ on 2019, Aug 30.
[vii] Australia Senate Community Affairs References Committee. (2018). *Science of Mitochondrial Donation and Related Matters* (27 Jun 2018). Canberra, Australia: Senate Printing Unit, Parliament House.
[viii] Australia Senate Community Affairs References Committee. (2018). *Science of Mitochondrial Donation and Related Matters* (27 Jun 2018). Canberra, Australia: Senate Printing Unit, Parliament House. Chpt 5: Regulations, p 96.
[ix] Australian Government. (2019). *Australian Government Response to the Senate Community Affairs References Committee Inquiry into: The Science of Mitochondrial Donation and Related Matters*. Retrieved from https://www.aph.gov.au/DocumentStore.ashx?id=cde08631-8178-4e89-b08e-c6a12ef28327 on 2019, Aug 30.
[x] NHMRC. (n.d.). *Mitochondrial Donation*. Retrieved from https://www.nhmrc.gov.au/mitochondrial-donation on 2020, Mar 18.

United States of America

14. Current US laws prohibit the Food and Drug Administration (FDA) from reviewing applications for 'research in which a human embryo is intentionally created or modified to include heritable genetic modification', which includes MGRT. In April 2019, a group of scientists, patient advocates, and bioethicists started working on draft policy recommendations to Congress, with the intention of persuading Congress to lift the ban on MGRT.[xi,xii,xiii]

Ukraine

15. An online news source reported in June 2018 that MGRT was being offered at a fertility clinic in Kiev. The article stated that the procedure was attempted in 21 women, of which 14 attempts failed.[xiv] The research team lead claimed that the use of PNT was pre-approved by an ethics committee and a review board at the Ukrainian Association of Reproductive Medicine, where he holds the appointment of Vice-President. In a subsequent media article, several UK experts were critical of the use of PNT as fertility treatment in the Ukraine.[xv]

Greece

16. On 11 April 2019, another research team announced the birth of a child through MST.[xvi,xvii] The team involved Spanish researchers who offered the technology through a fertility clinic in Greece.[xviii] The purpose of MST in this instance was to treat infertility, not to avoid the birth of a child with a mitochondrial disorder. In July 2019, the European Society of Human Reproduction and Embryology (ESHRE) issued a statement strongly recommending a moratorium on the use of MST as fertility treatment. In its statement, ESHRE noted that mitochondrial donation was originally intended 'for the treatment of women carrying life-threatening mitochondrial diseases to prevent the birth of affected children', and that 'the application of spindle transfer as a remedy for fertility treatment remains vague and unproven'.[xix]

V. The BAC's Assessment of the Current State of MGRT

17. In light of the developments described above, the BAC is of the view that it is premature at the present time to consider the acceptability of clinical application of MGRT, and *in vivo* research performed in human subjects in Singapore for the purpose of developing MGRT. While reviews conducted by the HFEA have deemed PNT and MST to be 'sufficiently safe to proceed cautiously and in restricted circumstances',[xx] the BAC notes that the UK is an outlier

[xi] Mullin, E. (2019, Apr 16). *Patient Advocates and Scientists Launch Push to Lift Ban on 'Three-Parent IVF*'. STAT News. Retrieved from https://www.statnews.com/2019/04/16/mitochondrial-replacement-three-parent-ivf-ban/ on 2019, Aug 30.

[xii] Adashi, E., et al. (2019). In Support of Mitochondrial Replacement Therapy. *Nature*, *25*, pages 870–871. DOI: 10.1038/s41591-019-0477-4.

[xiii] Petrie-Flom Center, Harvard Law School. (n.d.). *Mitochondrial Replacement Therapy: Considering the Future of U.S. Policy on 'Three-Parent' IVF* [Events-Lectures and Panels]. Retrieved from https://petrieflom.law.harvard.edu/events/details/mitochondrial-replacement-therapy on 2019, Aug 30.

[xiv] Stein, R. (2018, Jun 6). Clinic Claims Success in Making Babies with 3 Parents' DNA. *NPR*. Retrieved from https://www.npr.org/sections/health-shots/2018/06/06/615909572/inside-the-ukrainian-clinic-making-3-parent-babies-for-women-who-are-infertile on 2019, Aug 30.

[xv] Science Media Centre. (2017, Jan 18). *Expert Reaction to News of the Birth of a Baby in Ukraine Through Pronuclear Transfer as a Treatment for Infertility*. Retrieved from https://www.sciencemediacentre.org/expert-reaction-to-news-of-the-birth-of-a-baby-in-ukraine-through-pronuclear-transfer-as-a-treatment-for-infertility/ on 2019, Aug 30.

[xvi] Devlin, H. (2019, Apr 11). Baby with DNA from Three People Born in Greece. *The Guardian*. Retrieved from https://www.theguardian.com/science/2019/apr/11/baby-with-dna-from-three-people-born-in-greece-ivf on 2019, Aug 30.

[xvii] Betuel, E. (2019, Apr 13). Greece's '3 Parent Baby' Highlights Global Controversy Over the Technique. *Inverse*. Retrieved from https://www.inverse.com/article/54844-three-parent-babies-fertility-techniques on 2019, Aug 30.

[xviii] Parc Cientific de Barcelona, Universitat de Barcelona. (2019, Jan 17). *Embryotools Achieves the World's First Pregnancy with a New Nuclear Transfer Technique for Treating Infertility* [News]. Retrieved from http://www.pcb.ub.edu/portal/en/noticies/-/noticia/no_embryotools-aconsegueix-el-primer-embaras-del-mon-amb-una-nova-tecnica-de-transferencia-nuclear-per-tractar-la-infertilitat on 2019, Aug 30.

[xix] ESHRE. (2019, July 9). *Moratorium on the use of spindle transfer as fertility treatment* [Press Room-News and Statements]. Retrieved from https://www.eshre.eu/Press-Room/ESHRE-News on 2019, Aug 30.

[xx] HFEA. (2016). *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016*

on the global stage in this regard, as it is the only country which has developed regulatory controls and oversight to permit MGRT at the time of this writing.

18. As such, the BAC is of the opinion that it is premature to consider an exception to its 2005 recommendation not to allow clinical germline genetic modification, as would occur with MGRT, until such time as the BAC's concerns below are addressed.

Uncertainty surrounding the safety of MGRT

19. In the course of the BAC's public consultation exercise, safety was a widely raised concern in all community platforms (scientific, religious, as well as the general public). While respondents empathised with the plight of women known to transmit mitochondrial disorders to their children, those who did not in-principle oppose the use of MGRT expressed the view that it should only be permitted in Singapore if it were demonstrated to be safe, and in restricted circumstances.

20. The BAC agrees with and shares the concerns surrounding the safety of MGRT. Portrayal of mitochondria to the lay public as the 'battery pack' of cells, while not inaccurate, has oversimplified potential biological effects of MGRT. Mitochondria also play several other important cellular functions which are the subject of ongoing research.[xxi] Given this uncertainty, the BAC is concerned that manipulation of mitochondria in the MGRT process may cause unintended adverse consequences in the resultant child.

21. Stemming from the above, the BAC recommends awaiting the results of reputable international initiatives (such as those conducted by the UK's Newcastle Fertility Centre, and possibly others that follow). More specifically, there should be substantial evidence of short- and long-term safety and efficacy from such trials in other countries before revisiting whether MGRT for the prevention of severe mitochondrial disorders should be permitted in Singapore. Such evidence should address concerns pertaining to whether there may be trans-generational factors to consider, and if so, what they would be.

22. The BAC notes that there have been anecdotal 'success stories' of babies born with the assistance of MGRT in mainstream media internationally as described above. However, there has been little information about the health of such children, whether any follow-up investigations have been conducted, and whether any of these claims were verified and/or reviewed independently. At present, the only known approval of MGRT involving implantation and live birth is being conducted at the UK Newcastle Fertility Centre.[xxii] Even then, it may be some time before sufficient data to inform a view on safety become available.

Clinical efficacy of MGRT not established

23. The BAC acknowledges that replacement of affected mitochondria with healthy donor mitochondria has the potential to prevent the transmission of mitochondrial disorders in humans. However, this has yet to be verified rigorously as a consistent outcome in clinical studies with close follow-up of more than single cases. As mentioned in the MGRT consultation paper, even if MGRT were to reduce the amount of abnormal mtDNA in the modified embryo and the resultant child, the clinical efficacy of such reduction in preventing morbidity from mitochondrial disorders remains to be determined.[xxiii]

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update, p 43.

[xxi] Friedman, J.R. & Nunnari, J. (2014). Mitochondrial Form and Function. *Nature*, 505(7483), 335-343. DOI: 10.1038/nature12985.

[xxii] Newcastle University Press Office. (2017, Mar 16). *Newcastle Awarded World's First Mitochondrial Licence* [Press Release]. Retrieved from https://www.ncl.ac.uk/press/articles/archive/2017/03/mitochondrialicence/ on 2019, Aug 30.

[xxiii] In this interim report, references to the efficacy of MGRT refer to the extent to which MGRT techniques result in the *prevention of morbidity*

24. While there have been several reported births of children conceived through MGRT in recent years (in particular, Mexico, Ukraine and Greece), they shed little light on the efficacy of MGRT. For the children born in Ukraine and Greece, MGRT techniques were used as fertility treatment, and not to prevent transmission of mitochondrial disorders. On the other hand, while the mother of the child born in Mexico was a carrier of a mitochondrial disorder, the child's family did not allow the child to undergo further retesting for abnormal mtDNA beyond that performed while a neonate, resulting in a lack of objective longitudinal data.[xxiv]

VI. Ethical, Legal and Social Issues Pertaining to MGRT

25. In addition to the concerns relating to the safety and efficacy of MGRT described above, the BAC acknowledges that the present discussion raises several ethical, legal, and social issues. These are summarised below.

MGRT is preventive, not therapeutic

26. The BAC is of the view that MGRT is a preventive intervention, not a form of therapy.[xxv] This is a fundamental distinction as considerations of its importance in preventing mitochondrial disorders may differ if MGRT were regarded as the only recourse for alleviating the *actual* suffering of individuals. However, because MGRT is a technique which, if permitted, may prevent the birth of babies who would otherwise suffer from serious mitochondrial disorders, but cannot treat patients who suffer from mitochondrial disorders, the process of balancing the potential benefits against the potential risks takes on a different complexion as there are existing alternatives to MGRT.

27. The BAC's MGRT Consultation Paper set out several existing alternatives for parents seeking to prevent transmission of mitochondrial disorders to their future children.[xxvi] While these options have limitations and may not be considered optimal by all, the BAC is nonetheless of the view that, on the current evidence, the potential benefits of MGRT over these alternative options do not outweigh its potential risks.

Public acceptance of reproductive interventions and their implications remain varied

28. During the BAC's public consultation, a view that was substantially similar to the expressivist argument was raised in opposition to permitting MGRT.[xxvii] The BAC accepts without qualification that people with disabilities are of no less value than able-bodied people, and are similarly entitled to be treated with respect and dignity. However, the BAC is also of the view that the expressivist argument is similarly applicable to some assisted reproduction techniques already practised in Singapore involving embryo selection, and is not in itself determinative on the issue of whether MGRT should be permitted in Singapore.

29. In the discussion with representatives from the different religious groups in Singapore,[xxviii] several religious perspectives opposing MGRT were mentioned. They included concerns

from mitochondrial disorders in a resultant child.

[xxiv] Zhang, J. et al. (2017). Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease. *Reproductive Medicine Online*, 34(4), 361–368. DOI: 10.1016/j.rbmo.2017.01.013.

[xxv] Pompei, M. & Pompei, F. (2019). Overcoming bioethical, legal, and hereditary barriers to mitochondrial replacement therapy in the USA. *Journal of Assisted Reproduction and Genetics*, 36(3), pp 383-393. DOI: 10.1007/s10815-018-1370-7.

[xxvi] BAC. (2018). *Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology: A Consultation Paper*, pp 5-6, para 15-21.

[xxvii] The expressivist argument interprets the use of biotechnologies to prevent the birth of individuals with specific disabilities as an expression of disvalue for existing people with such disabilities.

[xxviii] Views from the following religious groups were received through either meeting participation or written representation: Hindu Advisory Board, Islamic Religious Council of Singapore (MUIS), Jewish Welfare Board, National Council of Churches of Singapore, Parsi Zoroastrian Association of Singapore, Roman Catholic Archdiocese of Singapore, Sikh Advisory Board, Singapore Buddhist Federation, Taoist Mission, The Spiritual Assembly of the Baha'is of Singapore.

regarding the moral status of the embryo, clarity of a child's lineage, and that MGRT may disrupt the concept of family and its resultant implications. However, some several religious groups did not object to MGRT as a means of preventing transmission of serious diseases, subject to concerns of safety and efficacy.

30. The BAC would like to extend its gratitude to representatives of all religious groups for their participation in the present discourse. As Singapore is a multicultural, pluralistic society with a wide range of religious perspectives, the BAC hopes that religious groups will continue to be active in, and contribute to ongoing bioethics discussions.

VII. Conclusion

31. The BAC's 2005 *Report on Genetic Testing and Genetic Research* states: We are of the view that the clinical practice of germline genetic modification should not be allowed at this time. Germline genetic modification is at present still experimental and will require substantial research to establish its feasibility and safety in clinical application. In addition, the potentially great impact on future generations presents serious ethical concerns.[xxix]

32. Given the concerns regarding the safety and efficacy of MGRT summarised in this interim report, the BAC is of the view that it is premature to exempt MGRT from prohibition of clinical germline genetic modification. As such, the BAC recommends that the clinical practice of MGRT and clinical MGRT-related research performed *in vivo* in human subjects should not be permitted at this time.

33. The BAC acknowledges that should MGRT be permitted in Singapore, significant ethical, legal, and social issues will be raised and debated. However, given that the BAC's 2005 position remains unchanged at this time, a more definitive discussion of these issues would be better undertaken at a future date when more certainty regarding the science, techniques, safety, and efficacy of MGRT is available.

[xxix] BAC. (2005). *Genetic Testing and Genetic Research*, p 37, para 4.52.

ANNEXE A

CONSULTATION PAPER: ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

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

A Consultation Paper

Bioethics Advisory Committee

Singapore

19 April 2018

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.[i] 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 32 and 33, respectively.

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).

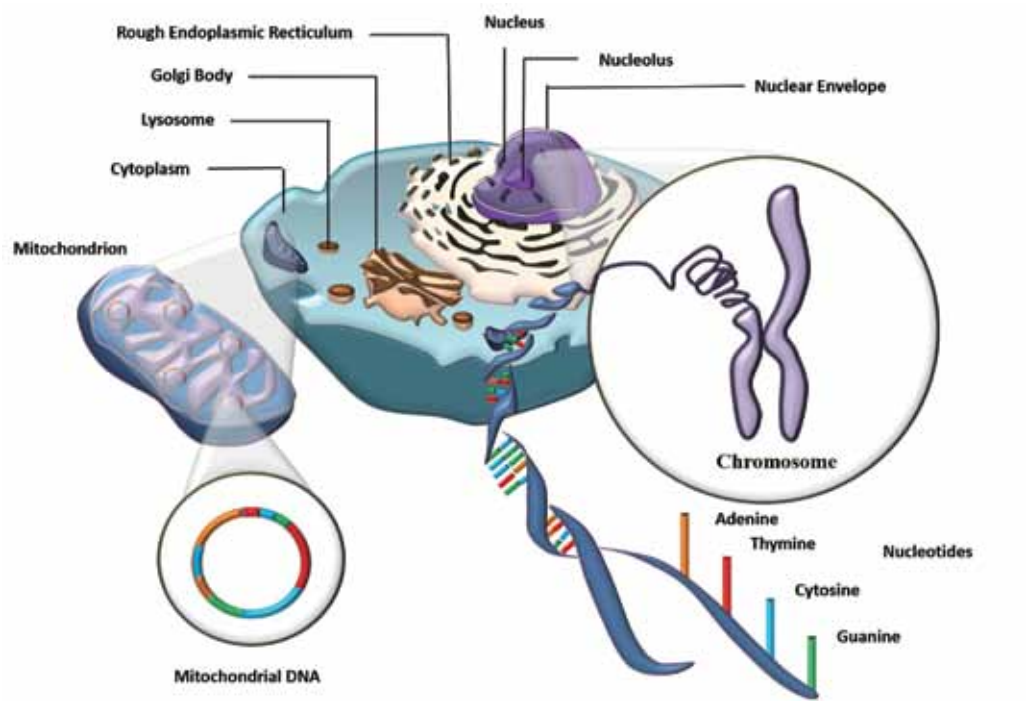
6. Most of the cell's DNA can be found within the nucleus of our cells. This is called the nuclear genome, which contains between 20,000 and 22,000 protein-coding genes. Genes are segments of the DNA sequence that code for inherited traits such as height and eye colour, blood type, muscle mass and the 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

[i] 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).

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.[ii] 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)



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,[iii] 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

[ii] 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.

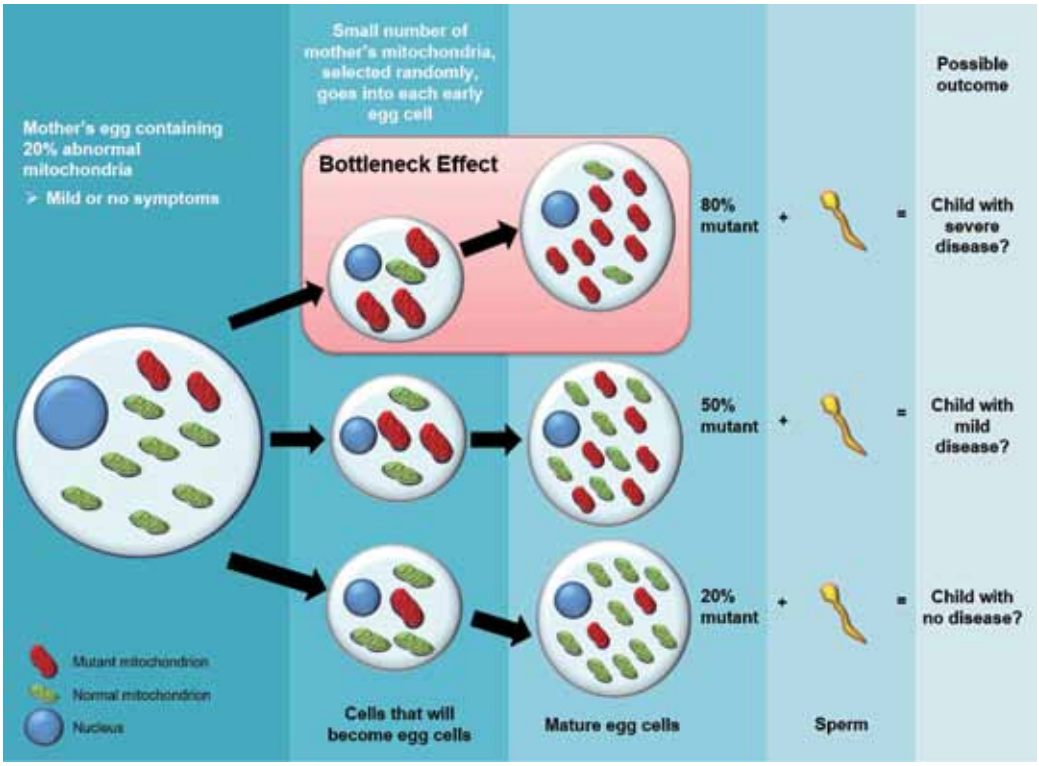
[iii] The mitochondrial genome contains 16,569 base pairs, while the nuclear genome has about 3,200,000,000 base pairs.

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.

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.[iv] 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 underdiagnosis or misdiagnosis.

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.[v] 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

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

[v] 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)

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 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.[vi] 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.

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

[vi] 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.

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.[vii] 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.[viii] 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.[ix] 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.

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.

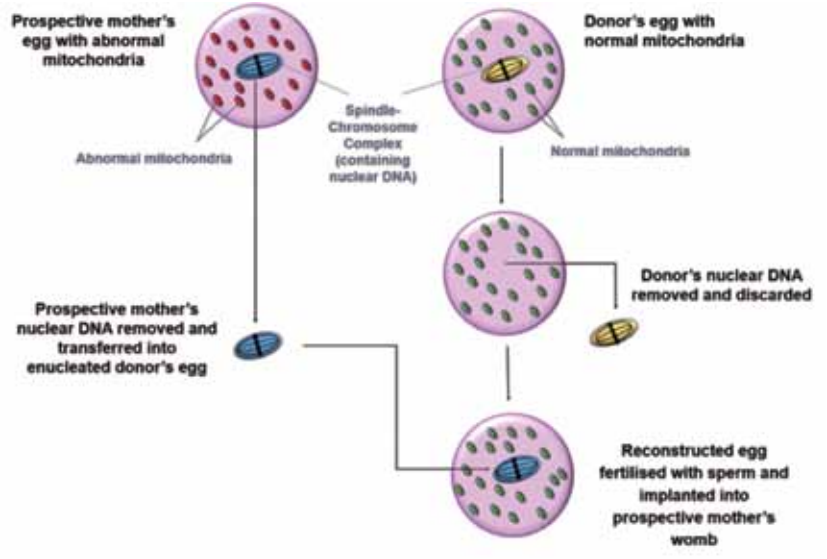
[vii] Though BAC considers MGRT to be a form of germline modification, there are important differences between MGRT and other germline therapies that alter the nuclear genome. The distinctions are discussed in detail in paragraph 76 of this paper.

[viii] UK *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*. Regulation 5.

[ix] 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.

Annexe A

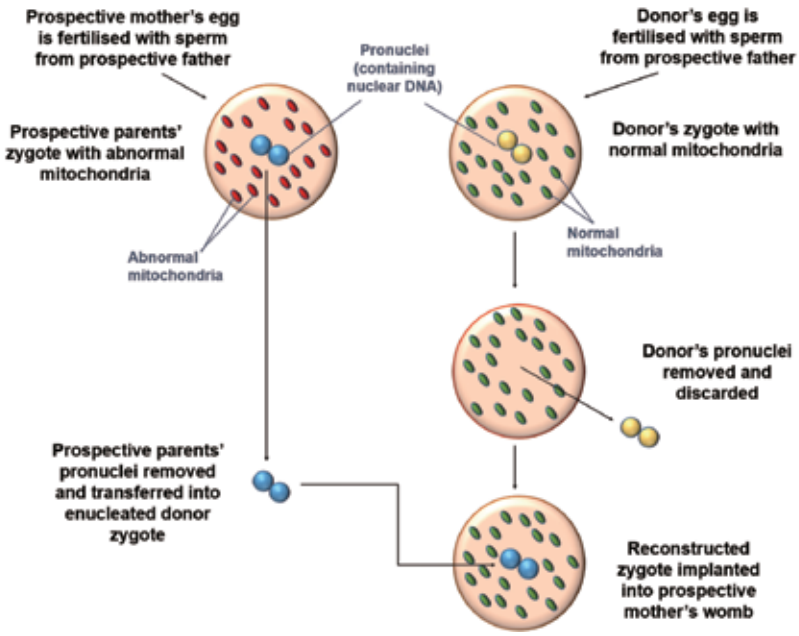
Figure 2.1: Maternal Spindle Transfer (MST) in Eggs
(Figure not drawn to scale. Modified from: Nuffield Council on Bioethics, UK. *Novel Techniques for Prevention of Mitochondrial DNA Disorders: an Ethical Review*. 2012.)



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[x] 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.

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.)



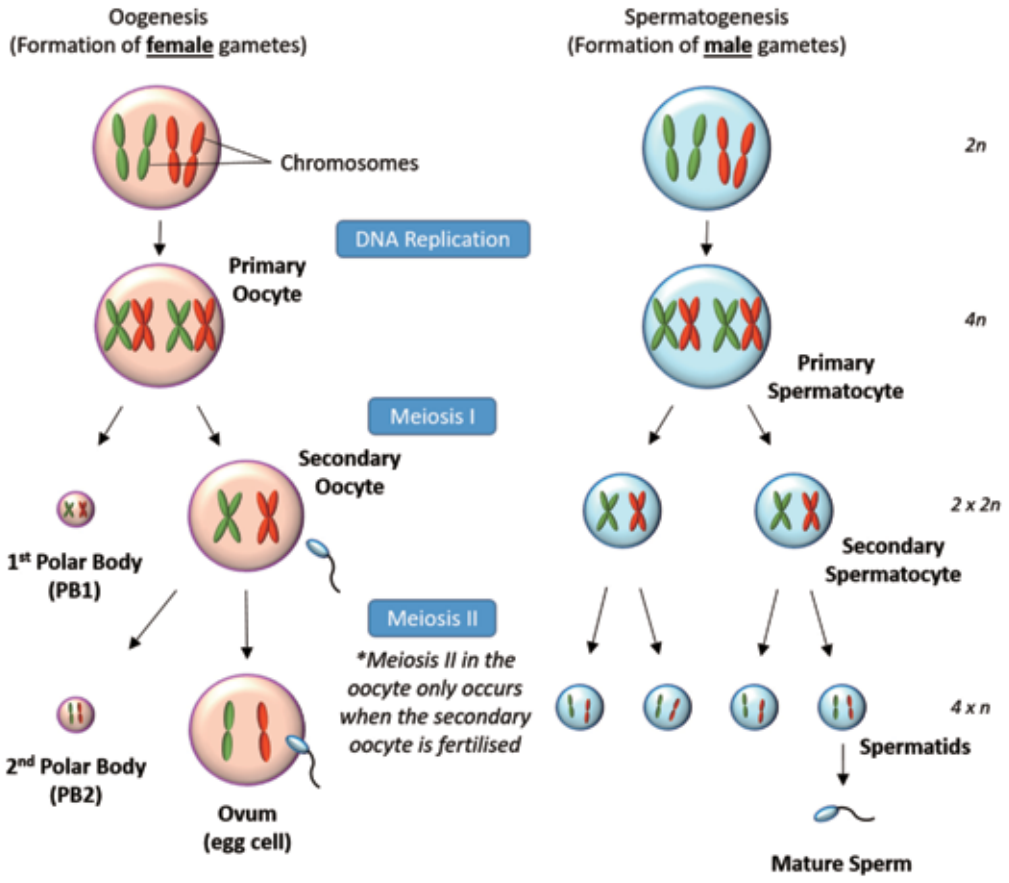
[x] The two pronuclei — one pronucleus from the sperm, and one from the egg — are structures visible in the egg from about 10 hours after penetration by the sperm at fertilisation. Each contains the father's and mother's transmitted genetic material respectively, before they fuse to form a zygote ready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

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)



Annexe A

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.)

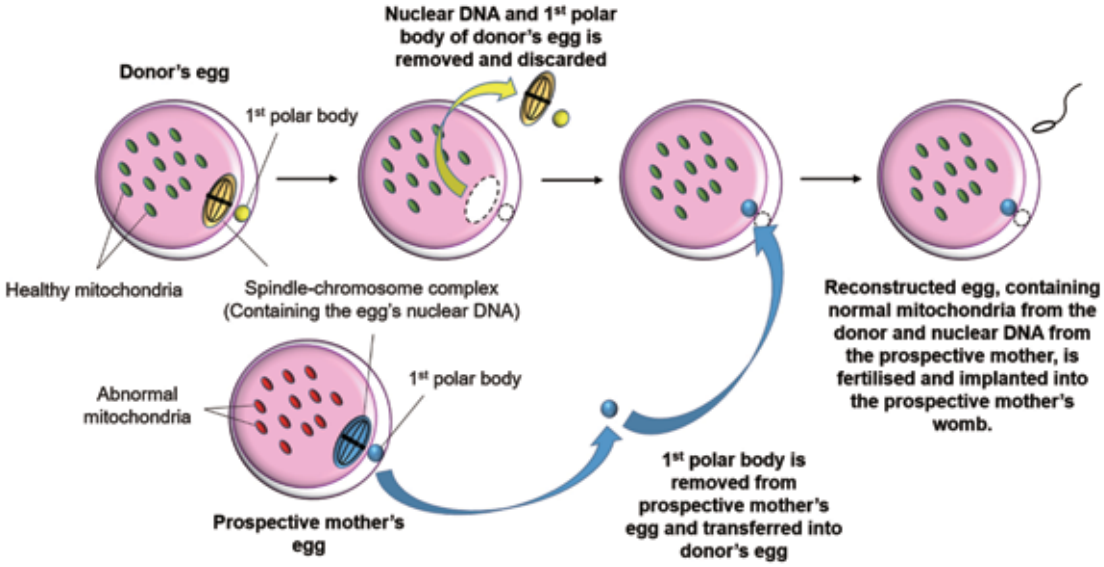
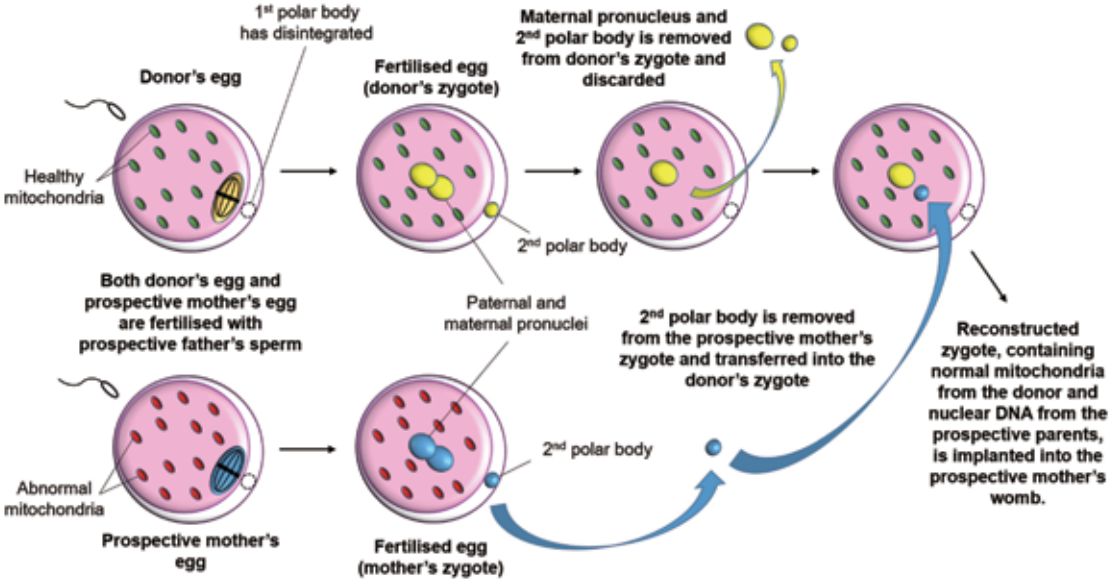


Figure 2.5: Polar Body 2 Transfer (PB2T)
(Figure not drawn to scale. Modified from: HFEA, UK. *Review of Safety and Efficacy of Polar Body Transfer to Avoid Mitochondrial Disease: Addendum to 'Third Scientific Review of Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 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,[xi] proving the feasibility of the technique. A three-year follow-up study on these monkeys showed normal growth and development, and no detectable abnormalities.[xii]

34. The potential feasibility of MST in preventing the transmission of abnormal mtDNA has also been demonstrated in human eggs.[xiii] 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.[xiv] 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.[xv] 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.

[xi] Tachibana M *et al.* Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells. *Nature.* 461 (2009): 367-372.
[xii] Tachibana M *et al*. Towards Germline Gene Therapy of Inherited Mitochondrial Diseases. *Nature.* 493 (2013): 627-631.
[xiii] *Ibid.* See also: Paull D *et al*. Nuclear genome transfer in human oocytes eliminates mitochondrial DNA variants. *Nature.* 493 (2013): 632-637.
[xiv] 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.
[xv] Zhang J *et al*. Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease. *Reproductive Biomedicine Online.* 34 (2017): 361-368.

Annexe A

PNT

35. PNT resulting in the live birth of normal offspring was first carried out successfully in mice in the early 1980s.[xvi] 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,[xvii] as well as in abnormally[xviii] and normally[xix] 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.[xx] 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.[xxi] 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.[xxii] 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.[xxiii] 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.[xxiv] Both babies were reported by the clinic to be healthy, though there have been no updates about their status since.[xxv]

PBT

37. To date, PBT studies have been conducted on mice[xxvi] and human eggs.[xxvii] As recent studies have indicated that reversion could be significant in MST and PNT,[xxviii] 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[xxix] and therefore a lower likelihood of reversion.

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

[xvii] 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.

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

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

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

[xxi] 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.

[xxii] 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.

[xxiii] 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)

[xxiv] 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)

[xxv] *Ibid.*

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

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

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

[xxix] 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.

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.'[xxx]

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'.[xxxi] 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.[xxxii]

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 Annexe 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.[xxxiii] This position was reiterated when the UNESCO International Bioethics Committee (IBC) reviewed the subject in 2003.[xxxiv] 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.'[xxxv]

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.'

[xxx] UNESCO. *Universal Declaration on Bioethics and Human Rights.* 2005. Article 16.
[xxxi] Bioethics Advisory Committee. *Genetic Research and Genetic Testing*. 2005. Paragraph 4.52.
[xxxii] National Medical Ethics Committee, Singapore. *Ethical Guidelines for Gene Technology.* 2001.
[xxxiii] UNESCO. *Universal Declaration on the Human Genome and Human Rights.* 1997. Article 24.
[xxxiv] UNESCO. *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention*. 2003. Paragraph 84.
[xxxv] UNESCO. *Report of the IBC on Updating its Reflection on the Human Genome and Human Rights*. 2015. Paragraph 104.

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,[xxxvi] 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]'.[xxxvii] As there was no universally agreed definition of 'genetic 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'.[xxxviii]

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.[xxxix] 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.[xl]

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

[xxxvi] 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.

[xxxvii] *Ibid.*

[xxxviii] 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.

[xxxix] 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.

[xl] 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)

are satisfied.[xli] 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;

(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.[xlii]

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.[xliii] 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.[xliv]

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.

[xli] 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.

[xlii] 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)

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

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

Annexe A

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.[xlv] 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 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

[xlv] 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.

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.[xlvi]

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.[xlvii] 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.[xlviii]

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.[xlix] Apart from the prospective parents and immediate future child, future 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

[xlvi] 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.

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

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

[xlix] 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.

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.[l] 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,[li] 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 healthy humans. Thus, the study predicts that it is unlikely that nuclear-mitochondrial DNA incompatibility bears any significant risk for MGRT.[lii] 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.[liii] 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.[liv]

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

[li] 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'.

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

[liii] 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.

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

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.[lv] 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.[lvi] Moreover, genetic identity is only one aspect of personal identity; the latter being dependent also on one's upbringing and life experiences.

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.[lvii] 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.[lviii] 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.[lix]

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)[lx] 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.

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

[lv] UK *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015* Regulation 11

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

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

[lviii] 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.

[lix] 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.

[lx] 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.

should have a reasonable chance of an acceptable quality of life, and the risks should be reduced as much as reasonably possible.[lxi] 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.[lxii]

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'.[lxiii] As such, it has been suggested that it would be appropriate to offer MGRT 'as a clinical risk reduction treatment for carefully selected patients'.[lxiv]

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,[lxv] 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.[lxvi] 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.

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.

[lxi] Bredenoord AL & Braude P. Ethics of Mitochondrial Gene Replacement : from Bench to Bedside. *BMJ.* 341 (2010): c6021.
[lxii] Dresser R. Designing Babies: Human Research Issues. *IRB: Ethics & Human Research* 26(2004) 1-8
[lxiii] HFEA, UK. *Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2016 Update.* November 2016. See p7.
[lxiv] *Ibid.*
[lxv] The relationship between abnormal mitochondrial load and manifestation of symptoms was discussed in paragraph 11 above.
[lxvi] *Ibid*, p39.

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.[lxvii] 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.

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[lxviii] and any new assisted reproductive service[lxix] 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.[lxx] 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

[lxvii] 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)

[lxviii] 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.

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

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

that both PNT and MST 'were sufficiently safe to proceed cautiously and in restricted circumstances'.[lxxi]

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.[lxxii] On the grounds of eugenics, MST is therefore the less ethically acceptable option than PNT.

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.[lxxiii] 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?

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

[lxxii] 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 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.

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

Annexe A

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**.

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.

Annexe A

Glossary

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.
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.

Glossary

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.

Annexe A

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Annexe A

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)** 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: (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)** 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)** 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)** 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)** 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).
India	'Soft' Ban *	**National Bioethics Committee, Ethical Policies on the Human Genome, Genetic Research & Services (2002)** Germline therapy in humans shall be proscribed, due to the present state of knowledge of the field. **Indian Council of Medical Research, Ethical Guidelines for Biomedical Research on Human Participants (2006)** Germline therapy is prohibited (p70).

Policies on Clinical Application of Human Germline Modification

Jurisdiction	Regulatory Position	Relevant Law or Guideline
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)** 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)). 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** 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*.
Japan	Ban	**Guidelines of Clinical Research Regarding Gene Therapy (2015)** 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)** 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)** 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)** 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)** Gene therapy on sperm, oocytes, embryos or foetuses is prohibited (Article 47(2)).

Annexe A

Policies on Clinical Application of Human Germline Modification

Jurisdiction	Regulatory Position	Relevant Law or Guideline
Sweden	Ban	**Genetic Integrity Act (2006)** 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. 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.
United Kingdom	Nuclear Genome Editing – Ban 'Mitochondrial' Replacement – Permissible under certain conditions	**Human Fertilisation and Embryology Act (1990, amended 2008)** It is prohibited to place in a woman gametes or embryos that have altered nuclear DNA (Section 3). **Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015** 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 * MGRT Research – Ban	**Consolidated Appropriations Act, 2017** 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. **Federal Notice on 'Final Action Under NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules' (March 2016)** The NIH will not at present entertain proposals for germ line alterations. (p15320) **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)** The FDA explicitly prohibits any clinical research that involves using MGRT in humans.

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

ANNEXE B

CONSULTATION PAPER DISTRIBUTION LIST

Annexe B – Distribution List for Consultation Paper on Ethical, Legal and Social Issues Arising from 'Mitochondrial Genome Replacement Technology' (Public Consultation Period: 20 April 2018 to 15 June 2018)

Institutions and Societies
Academy of Medicine Singapore
Alzheimer's Disease Association
Association of Women Doctors (Singapore)
Association of Women for Action and Research
Autism Association (Singapore)
Association of Women for Action and Research (AWARE)
Bioinformatics Institute
Bioprocessing Technology Institute
Catholic Medical Guild
Centre for Biomedical Ethics
Clinical Imaging Research Centre
Club Rainbow
College of Family Physicians Singapore
Epilepsy Care Group
Experimental Therapeutics Centre
Genetic Modification Advisory Committee
Genome Institute of Singapore
Health Promotion Board
Health Sciences Authority
Healthy Aging Association
Humanist Society
Institute of Bioengineering and Nanotechnology
Institute of Medical Biology
Institute of Molecular and Cell Biology
Muscular Dystrophy Association Singapore
NanoBio Lab
National Council of Social Service
Obstetrical and Gynecological Society of Singapore
Parkinson's Disease Society of Singapore (Renamed to Parkinson Society Singapore)
Rainbow Across Borders
Rare Disorder Society Singapore
Singapore Academy of Law
Singapore Association for Mental Health
Singapore Bioimaging Consortium
Singapore Cancer Society
Singapore Epilepsy Foundation
Singapore Immunology Network
Singapore Institute for Clinical Sciences
Singapore Medical Association
Singapore Medical Council
Singapore National Academy of Science
Singapore National Stroke Association
Singapore Paediatric Society
Singapore Psychiatric Association

The Caregivers' Association of the Mentally Ill
The Law Society of Singapore

Assisted Reproduction Clinics
Advanced Centre for Reproductive Medicine Pte Ltd
Centre for Assisted Reproduction Pte Ltd
Centre for Assisted Reproduction, Singapore General Hospital
Centre for Reproductive Endocrinology, National University Hospital
KKIVF Centre, KK Women's and Children's Hospital
NUH Women's Centre, National University Hospital
O&G Partners Clinic for Women
Raffles Hospital Fertility Centre
Sincere IVF Center
Thomson Fertility Centre
Virtus Fertility Centre
Women Fertility & Fetal Centre

National University of Singapore
A*STAR-NUS Clinical Imaging Research Centre
Centre for Translational Medicine
Department of Bioengineering
Department of Biological Sciences
Department of Paediatrics, Yong Loo Lin School of Medicine
Department of Pharmacology
Department of Pharmacy, Faculty of Science
Department of Philosophy
Department of Psychological Medicine
Department of Psychology
Department of Sociology
Duke-NUS Graduate Medical School
Faculty of Law
Lee Kuan Yew School of Public Policy
Life Sciences Institute (LSI)
NUS Graduate School for Integrative Sciences & Engineering (NGS)
Saw Swee Hock School of Public Health
Temasek Laboratories

Nanyang Technological University
Bioscience Research Centre
Lee Kong Chian School of Medicine
School of Biological Sciences
School of Humanities, Philosophy
School of Social Sciences, Psychology
School of Social Sciences, Sociology

Singapore Management University
School of Law
School of Social Science, Sociology

Annexe B

Singapore University of Technology and Design
Faculty of Humanities, Arts and Social Sciences

Other Tertiary Institutions, Clubs and Societies
Biomedical Engineering Society
Department of Physiology, James Cook University
Nanyang Polytechnic
Ngee Ann Polytechnic
NTU Current Affairs Society
NTU Humanities and Social Sciences Club
NTU Psychology Society
NTU Student Union
NUS Engin Club
NUS Law Club
NUS Life Sciences Society
NUS Medical Society
NUS Psychology Society
NUS Student Union
NUS Tembusu College
Pharmaceutical Society of Singapore
Republic Polytechnic
Temasek Polytechnic

Religious Organisations
Buddhist Fellowship
Catholic Archdiocese of Singapore
Hindu Advisory Board
Inter-Religious Organisation
Islamic Religious Council of Singapore (MUIS)
Jewish Welfare Board
National Council of Churches Singapore
Sikh Advisory Board
Singapore Buddhist Federation
Singapore Jain Religious Society
Singapore Taoist Federation
Taoist Mission (Singapore)
The Parsi Zoroastrian Association of Singapore
The Spiritual Assembly of the Bahá'is of Singapore

ANNEXE C

WRITTEN RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION

Annexe C – Written Responses to Consultation Paper On 'Ethical, Legal, And Social Issues Arising from Mitochondrial Genome Replacement Technology'

Organisations and Institutions

1. Catholic Medical Guild

2. Centre for Biomedical Ethics, National University of Singapore

3. Hindu Advisory Board

4. National Council of Churches of Singapore

5. National Medical Ethics Committee

6. Singapore Cancer Society

7. The Law Society of Singapore

Local Individual Responders

8. Member of the public

9. Mr Darius Lee

10. Ms Hillary Chua

11. Ms Isabel Lim

12. Ms Serene Ho

International Responders

13. Dr John B. Appleby

14. Dr Katherine Drabiak

1. Catholic Medical Guild

Catholic Medical Guild of Singapore's Response to Mitochondrial Replacement Technology (MRT)

Introduction

In his very recent address to the "Defending International Religious Freedom: Partnership and Action" Symposium hosted by the US Embassy to the Holy See, Vatican secretary of state Cardinal Parolin reiterated the Church's stand and urged among other things, cooperation between religious communities and state to work towards the common good:

"while showing mutual respect for their respective autonomies, there must be a positive collaboration between religious communities and the State. Although independent, both entities are devoted to the wellbeing of the human person who is both religious and a citizen. The greater cooperation between them will result in a more effective service for the good of all."

This does not come as surprise since the Church's response has always been one that is deeply "human", considering each individual person as "the way of the Church" and seeing her "sole purpose" as the "care and responsibility for man, who has been entrusted to her by Christ himself". In her concern, the Church proclaims the great dignity and worth of every human being and thus urges governments and lawmakers everywhere to safeguard and protect it, in particular, in the emerging field of biomedical research today:

"the dignity of a person must be recognized in every human being from conception to natural death. This fundamental principle expresses a great "yes" to human life and must be at the center of ethical reflection on biomedical research, which has an ever greater importance in today's world".

It is in such a pursuit of the common good that the considerations of the ethical, social and medical issues of mitochondrial replacement technology (MRT) are being made here. MRT, a form of assisted reproductive technology that involves preimplantation genetic screening of the mother, preimplantation genetic diagnosis of the embryo after fertilization and in vitro fertilization (IVF) in which the future baby's mitochondrial DNA comes from a third party, seeks to replace the faulty mitochondria of the mother with that of a donor's egg so as to prevent the inheritance of mitochondrial disease. Though its intentions are laudable, this technique is fraught with serious ethical and significant potential medical and social complications.

Ethical Problems Associated with MRT

1. Affront to the Dignity of and a Threat against Human Life

In 2008, the Catholic Church released an official document entitled Dignitas Personae, or *The Dignity of a Person*, explaining the ethical problems related to such artificial reproductive techniques. Underpinning these objections, it states, is that

"…the reality of the human being for the entire span of life, both before and after birth, does not allow us to posit either a change in nature or a gradation in moral value, since it possesses full anthropological and ethical status. The human embryo has, therefore, from the very beginning, the dignity proper to a person".

It is well known that embryo wastage in IVF is extremely high. Those with defects are directly discarded, while those that are not implanted in the mother's womb are either discarded or frozen

so that multiple pregnancy, which may be potentially harmful to mother and child(ren), may not occur. *Dignitas Personae* decries this "sad reality" as "truly deplorable", since "the "various techniques of artificial reproduction, which would seem to be at the service of life and which are frequently used with this intention, actually open the door to new threats against life".

Some forms of MRT treat human embryos as mere "laboratory material" or "lego pieces" such as when the donor egg is fertilized first and the resulting embryo destroyed for "spare parts", using only the healthy mitochondria and other parts of the cell to combined with nuclear DNA from another embryo to form a "three-parent embryo", affronting the dignity that is owed to human life. The Church's objection to human cloning is applicable here:

"to create embryos with the intention of destroying them, even with the intention of helping the sick, is completely incompatible with human dignity, because it makes the existence of a human being at the embryonic stage nothing more than a means to be used and destroyed. It is *gravely immoral to sacrifice a human life for therapeutic ends"*.

2. Dissociation of Procreation from the Personal Context of the Marital Act and a Weakening of Respect to Human Life

A second moral objection which is related to the first, is the Church's teaching that "it is ethically unacceptable to *dissociate procreation from the integrally personal context of the conjugal act:* human procreation is a personal act of a husband and wife, which is not capable of substitution". It warns that once the act of procreation of another human being is removed from the safety of the intimate love between husband and wife, and reduced to mere "production" of offspring in the laboratory, it leads to "a weakening of the respect owed to every human being" and "a blithe acceptance of the enormous number of abortions involved in the process of *in vitro*". It also appeals to researchers not to "surrender to the logic of purely subjective desires and to economic pressures which are so strong in this area", but to uphold instead "the sacred and inviolable character of every human life from its conception until its natural end".

For the same reason, intracytoplasmic sperm injection or ICSI is considered "intrinsically illicit" since it takes place "outside the bodies of the couple through actions of third parties whose competence and technical activity determine the success of the procedure. Such fertilization entrusts the life and identity of the embryo into the power of doctors and biologists and establishes the domination of technology over the origin and destiny of the human person. Such a relationship of domination is in itself contrary to the dignity and equality that must be common to parents and children".

3. The Dangerous Slope of Genetic Engineering and Pre-implantation Diagnosis

With regards to the question of whether or not MRT is a form of genetic engineering, proponents of MRT in UK and Singapore have sung the same tune, that MRT is not genetic engineering but more akin to organ transplantation where faulty mitochondria is swapped out for a healthy one. Yet, one cannot deny that MRT involves the exchange of genetic material, in this case, mitochondrial DNA, which makes it very different from kidney transplantation for instance, since genetic material has the potential to impact the formation of the human person that grows from the embryo and the potent possibility to be passed down to future generations with unforeseeable repercussions.

Proponents of MRT have also thrown out the criticism that such genetic manipulation could lead down a slippery slope of genetic engineering towards a dangerous eugenic mentality that has haunted our memories since World War II. Yet, MRT uses a technique which flings the door towards eugenics wide open – that of pre-implantation diagnosis, where embryos formed in vitro

undergo genetic diagnosis, followed immediately by the elimination of those suspected of having genetic or chromosomal defects. This technique could easily be, and likely have already been used by fertility clinics for eugenic purposes, eliminating embryos that do not have the desired sex of the child or those with unwanted qualities, especially when bred in an industry notorious for its nefarious and abhorrent scandals due to unbridled profit margins and little regulatory oversight. Thus the Catholic Church has denounced preimplantation diagnosis, "connected as it is with artificial fertilization", as "always intrinsically illicit", since it is "directed toward the qualitative selection and consequent destruction of embryos, which constitutes an act of abortion". It also warns that it is an "expression of a eugenic mentality that "accepts selective abortion in order to prevent the birth of children affected by various types of anomalies", and decries such an attitude as "shameful and utterly reprehensible, since it presumes to measure the value of a human life only within the parameters of 'normality' and physical well-being, thus opening the way to legitimizing infanticide and euthanasia as well".

4. The Looming Spectre of Human Cloning

The issue of whether or not MRT is considered a form of human cloning is still being debated. It is however not difficult to see why some experts have argued that it is indeed a form of human cloning since some forms of MRT involve the removal of an entire set of embryonic nuclear DNA from one embryo and transferred to another de-nucleated embryo.

If MRT were indeed an early form of therapeutic cloning, then every country would need to consider its implication more carefully and with greater gravity before sanctioning its use, since it is already well accepted that human cloning is morally objectionable and thus prohibited by not only the Catholic Church, but most developed countries around the world.

5. The Loss of Genetic Affinity and an Affront to the Human Good of Marriage

Experts have postulated that since mitochondria play an important role in many bodily processes, the genetic contribution of the donor might be significant: there are complex interactions between nuclear DNA and mitochondrial DNA and organelles contained in the cytoplasm might introduce epigenetic alterations in nuclear DNA. Others have posited that babies born through such techniques have the genetic material of three different parents and should be considered biologically tri-parental.

Since March last year, the concept of "genetic affinity" has been fleshed out as a basic human right when a couple who had used IVF to conceive a child, was awarded compensation by Singapore's supreme court after they discovered after the baby was born, that sperm from an unknown third party instead of her husband's had been used to fertilize the woman's ovum. The court explained that the woman's desire to have a child of her own with her husband "is a basic human impulse, and its loss is keenly and deeply felt", and her suffering was underpinned by a "severe dislocation of her reproductive plans that is constituted principally by the fracture of biological parenthood".

While parents who consent to MRT may not consider the introduction of a third party's genetic material in their child as a loss, the same cannot be said of the children who are born from such techniques. These children may face a profound "genealogical bewilderment" once they realize that their genetic make up was not solely of their parents but also involved the intrusion of a third party's genes. This poses a grave ethical problem since it goes against the fundamental human good of the unity of marriage, which in this case refers to "reciprocal respect for the right within marriage to become a father or mother only together with the other spouse", (now also known in legal terms as the right to "genetic affinity"), as well as the "specifically human values of sexuality which require "that the procreation of a human person be brought about as the fruit of the conjugal

act specific to the love between spouses" already elucidated in the previous section.

Breaching this crucially important ethical boundary would unsurprisingly lead to a plethora of medical and social problems such as existential and identity crises, emotional disturbances, depression and even possibly suicide, not to mention also the possible long term medical side effects from genetic tampering, as well as potential breakdown in marriages and families, divorce, lawsuits, crime and a myriad of other social ills that come with the break-up of society's most fundamental cell.

Potential Medical and Social Problems Associated with MRT

There are further potential medical and social concerns with regards to MRT. In the inquiries that took place before the implementation of MRT in the UK, there were some concerns that were not fully addressed by the Human Fertilisation and Embryology Authority (HFEA), the authority approving and governing the subsequent use of MRT in the UK. One was whether the embryo was at risk if there was a mismatch between the mitochondrial DNA haplotype of the mitochondria donor and that of the intending mother. The report by the HFEA in UK unsatisfactorily acknowledged that there was a lack of research evidence and that licensed clinics could consider haplotype matching as a precaution. The second poorly addressed concern was whether some of the faulty mitochondria would remain attached to the nucleus during the process of transfer as some scientific studies have shown. Although the panel did acknowledge that it is possible that mitochondria 'carry over' could occur potentially affecting the resulting embryo, they merely concluded that it would be unlikely to be problematic.

Then there is the issue of performing continued tests for these children, who may be made to feel like they are life-long "experiments" and thus abnormal, and also the real possibility that faulty DNA may be passed on to future generations via these procedures, potentially affecting their lives in significant ways.

To these grave concerns regarding MRT, one should also consider the well-known medical and social risks of IVF, one of the processes involved in MRT, which include anxiety, depression, or a lack of selfworth on the part of the mother when the process fails, which is significant given the very high failure rates. Some women also develop ovarian hyper-stimulation syndrome which may cause severe headaches and vomiting, psychiatric disturbances, or rarely, even death. It is also well documented that there are higher risks of congenital birth defects and increased prevalence of developmental disorders such as Beckwith-Weidemann and Silver Russell syndromes in the babies conceived through IVF.

At present there are insufficient studies into the long term complications of MRT. Simply allowing MRT with its inherent ethical problems, medical uncertainty and potential danger to the patient and the community, is at variance to our role as responsible scientists and physicians.

Conclusion

Given these serious ethical considerations and significant social and medical complications related to MRT, the Catholic Medical Guild of Singapore *strongly urge the Bioethics Advisory Committee to disallow mitochondrial replacement technology in Singapore until a more ethically sound, and medical and socially safe alternative is available.*

Such an ethical alternative to achieve a "cure" for mitochondrial diseases in children could hopefully be achieved when scientists are able to correct the mutated gene sequences themselves in the mitochondrial DNA while the egg is still inside the ovary, so as to avoid all the ethical conundrums

that are a threat to the fundamental goods of life, human dignity, procreation in marriage and genetic affinity that have been elucidated above.

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Annexe C

2. Centre for Biomedical Ethics, National University of Singapore

PUBLIC CONSULTATION ON ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

Submitted to the Bioethics Advisory Committee on 14th June 2018

by

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On behalf of the Centre for Biomedical Ethics, NUS

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

The Consultation Paper offers a very good summary of the potential benefits of MGRT for women who are carriers of mitochondrial disease. There are suggestions that other women may also benefit from MGRT (PNT in particular), although it is important to stress that the safety and efficacy of this technique has not been established. Careful study of the potential risks and benefits to children born with donor mitochondria in well-designed and supervised clinical trials is needed to fully appreciate the social and moral value of this technology.

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

The question posed assumes that genetic relatedness to parents is an important social and moral value. There is evidence to suggest that some members of Singaporean society strongly value genetic relatedness (e.g. the case of ACB v Thomson, the High Court). This assumption reflects the general willingness of parents to undergo the costs, discomfort and emotional stress of fertility treatment to have genetically related children, both in Singapore and abroad (Birenbaum-Carmeli, 2010), and indicates that genetic relatedness may for many be a particular need that cannot be achieved through adoption, for example.

However, the literature has challenged such assumptions about the value of genetic relatedness. For example, Baylis distinguishes between the 'needs' and 'wants' of parents to have genetically related children as having different moral value and argues that the latter is substantially less weighty (Baylis, 2017). Rulli has contested the suggestion that the mere biological mixing of genetic material between two parents can rise to the level of a substantial value or need (Rulli, 2016). Both have suggested that adoptive families can flourish without any genetic relatedness.

On the balance of these arguments, decisions about parenthood and value preferences for genetic-relatedness can be viewed as being deeply personal but also strongly situated within the social, politico-legal and economic contexts that provide parents with options for artificial reproductive technologies, such as MGRT, and access to alternatives, such as adoption.

3. Is it unfair to prevent women affected by mitochondrial disorders from access to new technology that offer them the potential to have healthy genetically-related children?

The answer to this question depends partly on whether the inability to have healthy genetically-related children due to mitochondrial disorders is recognized as a medical need. Commentators in the bioethics literature have argued against viewing it is a medical need (Baylis, 2017; Rulli, 2017), and based on BAC's Consultation Paper, it is unclear whether the BAC regards it as such. However, if it is recognized as a medical need, preventing women from accessing the technology may be unfair. This is because we generally allow access to new technologies (initially in closely-monitored trials) if they address medical needs and are otherwise regarded as safe, effective and without reasonable alternative.

However, a different scenario presents itself if a new technology merely helps to satisfy a personal (albeit important and deeply held) desire. In such cases, it is more debatable whether access restrictions would be conclusively unfair or, even if unfair, whether such restriction may be justifiable on other grounds. To illustrate this point, consider that many jurisdictions prevent unmarried women from access to IVF treatment. It may be argued that such restrictions are unfair as these unmarried women have the same desire as married

women to have genetically-related children. However, 'fairness' considerations might be viewed as less pressing here because (i) the technology does not address a medical need and (ii) there are non-trivial policy and cultural considerations that are considered to outweigh considerations of fairness. A similar argument could be made for the case of preventing or restricting access to MGRT: if the technology does not address a medical need and if there are sound ethical, legal and social concerns about its use (such as those considered in the BAC Consultation Paper), these could be considered to outweigh or counterbalance considerations of fairness.

4. Should the welfare of future generations take precedence over the welfare of existing individuals (i.e. the prospective parents), or vice versa?

We understand this question to be asking how we resolve conflicts between two duties: the duty to use MGRT only when it is agreed to be safe so that the welfare of future children is protected; and the duty to ensure prospective parents have prompt access to MGRT to realise their parental dreams/wishes/needs. There is general agreement throughout the literature that the safety of such technologies needs to be secured before such technologies are clinically adopted.

We would like to take the opportunity here to also comment on a related statement in Paragraph 59 of the Consultation Paper that we view as potentially confusing because two separate issues are conflated:

"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".

It is helpful to bear in mind that the use of MGRT in the clinical context would result in an entirely different child than the child that would have come about had MGRT not been employed.

The aggregate well-being of individuals would improve with the use of MGRT, not because existing people's lives are improved. Rather, it would be because healthier people come into existence. Prospective parents would also benefit from fulfilling their desire to have genetically-related children with no mitochondrial defects. Furthermore, there could also be substantial healthcare savings in the long-term.

5. What psychological or social impact might MGRT have on children born using such techniques?

A proven and reliable schema to predict the effects of novel biotechnologies on diverse societies has not been developed.

6. Is it true that children conceived through MGRT will have 'three parents'?

Analyses of the ethical acceptability (or not) of any new technology rely heavily on an accurate understanding of the science involved. Of equal importance in discussing new technologies is the discourse surrounding both scientifically complex but also ethically nebulous issues. These issues are particularly prominent in discussions of 'three-parent babies'.

The term 'three-parent baby' has caught on in the popular media. Such terms are adopted both to facilitate conceptualization of complex scientific processes but also to form part of the narrative which influences governments and public opinion for or against certain positions (Turkmendag, 2018). As noted in the Consultation Paper, some have critiqued the use of the term as misleading.

When discussing the concept of 'parent', there are in fact two separate concepts to be considered: one from the perspective of genetics, i.e. parentage, and the other from a social perspective, i.e. parenthood. Are we to consider 'parents' all those who have contributed genetically or are we to consider parents those who have reared a child even if they are only legally and socially linked to the child? A consideration of how such issues have already been addressed in children born of IVF treatments and in adoption would be helpful when considering this issue as it relates to MGRT.

It has been suggested that mitochondrial DNA consists of only a very small fraction of one's overall genome, and that while mitochondria are crucial for cellular function they have a relatively limited impact on phenotypical traits like appearance and behaviour that are more central to personal identity (Haimes & Taylor, 2015). According to this view, the impact of the third donor's DNA is relatively limited and constrained so as not to warrant the donor being given the status of 'parent'. The '…quantitative reasoning which uses a percentage calculation of DNA transmitted through the mitochondrial donation as a base for determining the donor's relational status to the offspring' has been viewed as misleading (Turkmendag, 2018). Conceptualizing and discussing the mitochondrial contribution in this manner also fails to recognize the scientific facts emerging around the function of mtDNA (Picard & McEwen, 2014; Ridge & Kauwe, 2018). In addition, it affects the public's perception of the rights children born of these technologies have to know their genetic origins and the legal status of the donor and it promotes the misleading view that mitochondrial donations are akin to organ donations (Haimes & Taylor, 2015; Turkmendag, 2018).

Some members of society will conceive of a link to a third individual via mitochondrial DNA as important and weighty (Jones, 2015). Others argue that MGRT is wrong in virtue of involving an 'unnatural' three-person genetic relationship (Caldwell, 2015). The objections to MGRT on the basis that it results in a 'three-parent baby' are similar to the objections to IVF more generally, which also involves three individuals and a process of conception facilitated by science. When a donor sperm or egg is used, there are in a sense three 'parents': the couple who sought IVF treatment, and will raise the child as their own, as well as a third-party donor who could accurately be described as a genetic parent. It must be asked whether it would be consistent to justify a prohibition of MGRT based on 'objectionable' 'three-parent' relationships when similar relationships are entailed by forms of IVF that are permitted.

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

What benefits MGRT trials produce depends heavily on how many people would eventually utilize the technology. If there is little demand for the use of MGRT, then both the risks to future people and the resources put into first-in-human trials may not outweigh the benefits. To substantiate this evaluation, more data is needed on the likely demand for MGRT and the cost of infrastructure and regulations needed to make MGRT trials viable in Singapore.

As the Consultation Paper notes in paragraph 38, there are no known MST, PNT or PBT projects currently being conducted in Singapore. The BAC Consultation Paper only cites the general incidence of mitochondrial disorders. There is some critical literature questioning

how many individuals would take up the technology even if it were viable. For example, Baylis suggests that the maximum number of live births via MGRT would stand at less than 15-22 per year in the UK (Baylis, 2017), which has about 695,000 annual births. Since Singapore has a much smaller total population, the potential uptake might be much smaller than UK estimates. This could make it difficult to enroll a meaningful sample of volunteers for a trial in Singapore.

Calculations of the cost for such treatments in the clinical context may also be a relevant consideration for commencing first-in-human clinical trials, especially if we ultimately seek to make this technology available to all those affected. The following is the estimated cost according to one source:

'…a successful conception is expected to require four cycles, as the success rate is estimated to be 25% per cycle. In this case, this means that the estimated cost of successful mitochondrial donation treatment, i.e. that resulting in a birth, if future intending mothers do not present any fertility problems, would therefore be approximately £80,000. This will of course vary according to the provider, to the efficiency of the treatment.' (Herbrand, 2017)

If first-in-human trials are to be undertaken in Singapore, a set of governance procedures should address the following considerations to guide an ethically responsible trial design:

- requiring Singaporean residency to ensure adequate follow-up
- ensuring adequate informed consent, including specific consent from the donor for MGRT
- in addition to IRB review, there should be a Ministry of Health review panel with experts on the scientific and clinical aspects of MGRT
- only facilities with proven capabilities should carry out MGRT procedures
- whether initially MGRT trial enrollment should be offered only to women who suffer from mitochondrial diseases or whether it may also be offered to other women who could benefit from its application (see response to Q1 in this document)

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

Various international responses to the question of whether MGRT constitutes an objectionable germline modification have been given. For instance, the UK has insisted that it is not a genetic modification because such debates and prohibitions over genetic modification were originally designed in the context of nuclear DNA modification, and are not applicable to mitochondrial DNA. In contrast, the US currently holds the converse position that it is a germline modification, on the grounds that mitochondrial DNA is potentially inheritable (at least from a mother; the National Academy of Sciences recommended that MGRT not be considered germline modification if used to create a boy, but the government has not taken up this recommendation) (Scott & Wilkinson, 2017).

It may be pressed that allowing MGRT, even if permissible in its own right, starts us down a slippery slope to more objectionable forms of germline modification, towards 'designer babies' with traits and features tailored to suit the arbitrary aesthetic whims of their parents. Slippery slope arguments are sometimes problematic, insofar as they rely on ungrounded speculation that engaging in one course of action potentially leads us to take an extreme. This is not always the case; allowing therapeutic cloning has not led us to permit reproductive cloning. Governments can and do draw reasonable boundaries on permitted and required courses of action in all domains of public policy.

Nevertheless, there are related concerns that should be taken seriously. It could be that MGRT, after being practiced for several years, (if there are no major adverse outcomes) causes a general societal shift in attitudes towards germline modification, normalizing genetic modification and making it appear to the general public more permissible. But it is also possible that the opposite will occur; a child born of MGRT has serious medical complications, and society becomes much more suspicious of genetic modifications going forward. It is also a further question of whether society becoming more permissive towards genetic modification is a bad thing.

A further consideration relates to consistency: if the government were to permit MGRT, there would be no in principle reason to prohibit direct modification of deficient mitochondria via a process like CRISPR, should there be sufficient evidence of safety and efficacy. Errors from such a process would be just as inheritable, and it would even avoid the presence of a third-party genetic donor that some find objectionable. This may raise the question of whether such mitochondrial modification clinical trials should be allowed as well. Again, it is a further question whether permitting such gene editing is acceptable.

9. 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?

We believe this ethical debate concerning this question is adequately addressed in the Consultation Paper.

In addition to the above responses, we would also like to raise several additional points for consideration:

10. Does MGRT contravene the prevailing Human Cloning Act?

Under Singapore's Human Cloning Act, paragraph 7 reads: 'No person shall develop any human embryo, that is created by a process other than the fertilisation of a human egg by human sperm, for a period of more than 14 days'. It can be argued that PNT contravenes this part of the act. The final stage embryo that is created in PNT is a result of replacing the pronucleus of a fertilized egg with the pronucleus of the prospective parent's fertilized egg. The new embryo is arguably not identical to either of the two initial embryos that we began with (Liao, 2017). Hence, PNT could be seen as a creation of a new human embryo by a process other than fertilization. This raises the question of whether PNT would contravene the prevailing Human Cloning Act.

PNT was not at all what was envisaged when the Human Cloning Act was passed in 2004. Nevertheless, the language as written could be interpreted as prohibiting PNT.

11. What empirical evidence regarding levels of support for such technologies is available?

There is limited empirical evidence for levels of support for MGRT from those affected directly or indirectly by mitochondrial disease or from the general public. There is no such empirical evidence relating specifically to Singapore. In the Appendix we refer to some empirical evidence from a number of jurisdictions.

We believe it would be beneficial for Singaporeans to be engaged in discussions about MGRT and for policy makers to have a sense of community views on issues associated with such technologies. The present consultation provides some opportunity for public input,

but a systematic survey, qualitative research, or community consultations would provide greater insights into broader perspectives on this important issue.

12. How does the framing of issues relating to MGRT impact on public perceptions?

The way information around these technologies has been framed in public and policy discussions has received attention. This is an important issue as it impacts on the public's response to and acceptance of the various stakeholder positions (as noted above in discussing 'three-parent babies'). An example of the framing of such issues and its implications for transparency and decisions made is provided by Turkmendag (Turkmendag, 2018). She suggests that mitochondrial donors have been equated to tissue donors (and as a result conceived as such by many members of the public) to assist in overcoming the donor shortage in the UK. The public's adoption of the 'tissue donor' conception of mitochondrial material can be seen in the public's responses to a call for evidence on Exploring ethical issues in biology and medicine (The Nuffield Council on Bioethics, 2012).

An issue pertaining to MGRT which has influenced the public's conception of the scientific facts and diverted attention from core ethical considerations includes the battery analogy. This analogy aims to significantly downplay not only the role of mtDNA but also the role of the donor (Turkmendag, 2018). Numerous scientists view the analogy as a distortion of scientific facts despite the abundance of scientific evidence available. In a 2014 submission to the House of Commons Science and Technology Committee, the Director of the Centre for Genetic Diseases at Monash University, Prof St. John, indicated the following:

'It is not appropriate to merely suggest that the mitochondrion and the mitochondrial genome influence energy within the cells, they have a far more sophisticated role to play during development. It is well documented in the literature that mitochondrial DNA haplotypes predispose or protect individuals against severe diseases such as cancer [(Shen et al., 2011)], diabetes [(Liou et al., 2012)], Parkinson's disease [(Ghezzi et al., 2005)] and many other neurological disorders.' (House of Commons Science and Technology Committee 2014, 35, emphasis in original)

It has also been suggested that the battery analogy downplays the ethical issues raised by changes to the germline (Turkmendag, 2018).

The way these issues are discussed impacts on the transparency of such discussions and our consideration or not of accepted scientific facts. Ultimately, this impacts on the level of transparency and respect shown for persons in policy decisions.

13. What insights do we gain from discussions around disability?

When talking about MGRT, we refer to mitochondrial disorders, diseases, or dysfunction. Such descriptors could be viewed as diminishing the value of those individuals whose mtDNA could produce inheritable genetic differences or those individuals who are already living with the effects of such differences. The way such genetic differences are discussed may raise for some concerns that the messages sent are hurtful and discriminatory in the same way that prenatal testing is viewed by some (Parens & Asch, 2003).

Similar concerns will also apply in the debate over preimplantation genetic diagnosis (PGD). In both PGD and MGRT, there is a practice of selecting an embryo over another and, in the process, some value judgement is made. In the case of MGRT, prospective parents select the embryo with the smallest percentage of abnormal mtDNA. Hence, the ethical

issues affecting the disability community with respect to PGD, such as the discriminatory messages being sent to disabled persons, would also be similarly present in MGRT.

There are scholars who support the value that disability (genetic diversity) brings to life (presumably viewing it as having instrumental value) (Garland-Thomson, 2012). Garland-Thomson also warns against stances arising from notions of alleviating suffering:

'When we imagine ourselves as charged with the mission of relieving the suffering of others, it is all too easy for projection to overtake empathy and for our own failure to imagine living with disability to lead to alleviating suffering by eliminating the person with a disability.' (p. 350)

Against such views, Sparrow reminds us of a cognitive bias known as 'status quo bias', which leads us to place greater value on things as they are and as we know them and leads us to believe that things should be as they currently present (Sparrow, 2015). Such a bias leads some to oppose technologies such as MRT. Sparrow concludes that the moral significance of preserving genetic diversity is ultimately undermined by our unwillingness to impose genetic diversity.

It is also important to attend to the voices of individuals directly or indirectly affected by mtDNA disorders, who do not see attempts to prevent its transmission as discriminatory (The Nuffield Council on Bioethics, 2012).

14. Alternatives to having genetically-related children

A number of options currently exists for women carrying abnormal mtDNA who wish to have healthy children and the Consultation Paper discusses several of these in paragraphs 15-21. However, one option that is currently not discussed is that of 'becoming a foster parent'.

We acknowledge that this option would not fulfill a woman's desire to carry a genetically-related child to term (as is also the case with adoption and IVF using a healthy donor egg). In addition, foster parenting is usually intended to be a temporary arrangement, thus frustrating the desire of potential parents to have their 'own' child. However, in comparison with adoption foster parenting comes with significantly shorter waiting times and it has been acknowledged by the Ministry of Social and Family Development, Singapore, that there is an unmet need for more individuals to foster children. Moreover, foster parenting, even if temporary, might still allow potential parents to develop a meaningful relationship with a child that is placed under their care. In light of these considerations, foster parenting merits mentioning, even if ultimately rejected by potential parents.

Concluding remarks

As the BAC Consultation Paper makes clear, there are numerous ethical issues that require careful consideration before MGRT could be considered for clinical practice. The first step towards any such consideration would be the conduct of trials. The decision whether to permit MGRT trials in Singapore depends on a variety of factors, as is clearly articulated in the BAC's Consultation Paper. We feel that two points should receive particular attention before any such decision is made:

1) More data should be gathered to estimate the likely uptake of MGRT in Singapore, both in the setting of a trial and, subsequently, in the clinical setting. As the Consultation Paper notes

in paragraph 38, there are no known MST, PNT or PBT projects currently being conducted in Singapore. Moreover, extrapolating from UK data, the clinical uptake of MGRT might be very small, given Singapore's population size. There is further uncertainty on how many individuals would be prepared to enroll in first-in-human trials. These considerations need to be weighed against the cost of infrastructure and regulations that are needed to make ethically responsible MGRT research viable in Singapore.

2) The BAC identifies the option to have 'healthy genetically-related children' as a potential key benefit of MGRT (paragraph 53 of the Consultation Paper). Accordingly, the answer to the question of whether to allow MGRT (in research or the clinical setting) will depend heavily on how much weight is attributed to this. The theoretical bioethics literature remains divided on how much, if any, value there is in a genetic relationship between parent and child. Moreover, only few empirical studies have gathered data on how much importance people actually attribute to genetic relatedness and there is no data yet that gives insight into the local Singaporean context. We recommend that empirical data be gathered to clarify this issue.

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Annexe C

Appendix - Empirical evidence relating to MGRT

Country	Year	Kind of evidence	Main points
UK	2013	Public Consultations Human Fertilisation and Embryology Authority, Mitochondria replacement consultation: Advice to Government, March 2013	There is overwhelming public support for MGRT with respondents expressing greater concern about safety issues than about associated ethical concerns. The public's support for such technologies arose from the consideration that MGRT provides the opportunity for parents to have genetically related children free from disease. In these consultations, there was also a general expectation that a strong regulatory system must be in place if such technologies are to be used in clinical practice.
UK	2018	Research findings Herbrand, C. and Dimond, R. Mitochondrial donation, patient engagement and narratives of hope. Sociology of Health & Illness, May 2018, Vol.40(4), pp.623-638	Further analysis of a subset of study participants involved in two separate UK studies has revealed additional insights into how women affected by mitochondrial disease respond to the emergence of such technologies. The analysis published in 2018 involved 22 women aged between 19-44 and at risk of transmitting mitochondrial mutations. All but three supported UK legislation for mitochondrial donation. Even though the majority supported the legislation, they did not all intend to make use of the technologies available. Support for these technologies related to hope for three groups: hope for their own procreation plans, hope for their children, and hope for society more broadly.
Australia	2017	Citizens' jury In Submission 29-Newson: Inquiry into the Science of Mitochondrial Donation and Other Matters	In 2017 an Australian citizens' jury was held to respond to the question: "Should Australia allow children to be born following mitochondrial donation?" The jury comprised 14 members of whom 8 were men and 6 women. The jurors had a range of ages and represented a variety of different cultures. All but 6 jurors held a university qualification. The majority view was that Australia should allow children to be born following mitochondrial donation but some attached conditions to this and some were not in agreement. Key areas of focus for jury participants were the scientific facts, the safety evidence in mitochondrial replacement technologies, the rights of those born as a result of mitochondrial donation, including the right to know one's genetic origins. Jurors also expressed the view that these technological developments were rapid.
Australia	2017-2018	Research findings In Submission 20-Mills, Ludlow, Sparrow, Warren: Inquiry into the Science of Mitochondrial Donation and Other Matters	An ongoing government funded Monash University research project examining legal and ethical issues relating to inheritable genetic modification in the Australian context includes the views of Australian scientists, policy makers, disability representatives, and people living with mitochondrial disease. In this study participants also view the safety of mitochondrial donation as paramount
US	2015	Research findings Engelstad, K. Sklerov, M. Kriger, J. et al. Attitudes toward prevention of mtDNA-related diseases through oocyte mitochondrial replacement therapy. Human Reproduction, 2016, Vol. 31(5), pp.1058-1065	This US study comprising 92 female carriers of mtDNA and 112 healthy oocyte donors, 95% of carriers felt that the development of oocyte mitochondrial replacement therapy was important and 97% of healthy oocyte donors were willing to donate oocytes that would lead to developing a viable embryo with the use of this technology.

3. Hindu Advisory Board

To: Bioethics Advisory Committee

Views on Mitochondrial Genome Replacement Technology

Our views are made in the context of the current prohibition of clinical germline modifications and that this proposal for mitochondrial genome replacement studies in humans, at this stage, is only for scientific studies.

We are in support of a carefully supervised study/research to try mitochondrial genome replacement technology in humans and our views are based on the following:

1. The intention of this research in humans is to develop technique(s) to prevent mitochondrial disorders being inherited in the new born. There is currently no treatment for such inherited lifelong disorders.

2. In as much as medical and biomedical research and tests have developed procedures and medicines for the treatment of various medical conditions so that humans can lead a healthy and meaningful life, medical research for the prevention of inheritance of severe disease and impairment at birth can be supported, as it benefits mankind.

3. It not against the principle of "ahimsa" or a negative effect on the natural order of life, at this study stage.

However such research has to be carefully staged and supervised so that the full effects of the application on humans can be fully understood. All the concerns that have been raised, and have led to the prohibition of clinical germline modifications, must similarly be fully allayed in this study. A primary concern would be that mitochondrial genome replacement technique may have an effect on the nuclear genome (germline modification) and thus the inherited characteristics from the parents. This has to be clearly proven not to be the case in this study. If at any stage it is proven otherwise, then the procedure should not be allowed to proceed as it would lead to the manipulation of the natural order of the cycle of human life and death and then to greater (unknown and irreparable) harm to humankind.

Thus it would be prudent for Singapore to take a collaborative approach with other similar research work being done elsewhere. This work has to be closely monitored, so as to gain sufficient understanding and confidence of the outcomes to ensure no unwarranted or undesirable effects on the nuclear genome. To fully appreciate the effects of such techniques on future generations will naturally take time as the effect on a single generation may not be conclusive, similar to other genetically derived characteristics.

Feedback on the questions raised:

1. Do you think that MGRT should be considered in Singapore? Why or why not?
   As stated above it can be considered after monitoring work done elsewhere.

2. Why is having the option to have genetically related children important?
   This is a natural human instinct that drives the cycle of human existence.

Annexe C

3. Do you agree that sufferers of mitochondrial disorders should have fair access to any technology that may potentially eliminate the disease in their children and future generations?
   Agreed, on condition that such genetic manipulative technology does not result in greater damage or harm to future generations of mankind.

4. What are your views on the welfare of future generations in the context of clinical trials involving MGRT? Whose interests should we give precedence to – future generations or existing individuals?
   Concern about the greater harm to future generations must take precedence over a few present individuals. That would be line with the sustainability of humankind and future societies. However if work is limited to only clinical trials or controlled trials to fully understand the effect and consequences, it can be allowed to gain further information.

5. What psychological or social impact might MGRT have on children born using such techniques?
   Though the answer would be somewhat speculative at this stage, it would be unlikely to be any more severe than for example a child finding out at a stage in his/her life that he/she is an adopted child and the parents are not biological parents. Another example would be children born from IVF techniques with anonymous donors.

6. Do the possible benefits justify first-in-humans trials of MGRT?
   Yes. However it is important that it is controlled and closely monitored.

7. Will allowing MGRT create an unethical exception to the prevailing prohibition on altering the human germline?
   Yes it would be an exception. The work can proceed as long as the work is strictly limited to

   a. Understanding how the procedure can prevent inherited severe lifelong illness.

   b. Establishing that this procedure has no other germline modification effect on next and future generations.

Hindu Advisory Board
28th Oct 2016

4. National Council of Churches of Singapore

The Ethics of Mitochondrial Replacement Technology: A Response by the National Council of Churches of Singapore to the BAC Consultation Paper Entitled, 'Ethical, Legal and Social Issues Arising From Mitochondrial Genome Replacement Technology'

BACKGROUND

The term 'Mitochondrial disease' refers to a broad range of disorders associated with the dysfunction of the mitochondria – organelles or tiny sub-units of every human cell except the blood cells. There are around 150 diseases associated with anomalies in either the mitochondrial or nuclear genome caused by inheritable mutations in the mitochondria. Studies have indicated that the incidence of people suffering from mitochondrial disease ranges between 1 in 4,300[i] and 1 in 6,000.[ii] The symptoms of these diseases range from mild to severe.[iii] There is currently no cure for mitochondrial disease, but many of the symptoms are treatable, and many people with mitochondrial disease 'have a normal life span with their disease well managed'.[iv] The prevalence of inheritable mitochondrial disease in Singapore has not been studied.[v]

Mitochondrial Genome Replacement Technology (MGRT) is an in vitro fertilisation technique that uses the mitochondrial DNA of a healthy donor to try to prevent the transmission of mitochondrial disease from the mother to her genetically related children. This technique is controversial because it is a form of germline modification that alters the genome of the offspring that will in turn be passed down to its progeny. On October 29, 2015, the United Kingdom became the first country to legalise this technique. On 16 March 2017, the UK Human Fertilisation and Embryology Act approved the first treatment license for the clinical application of MGRT.

In Singapore, the Bioethics Advisory Committee (BAC) conducted a closed-door consultation on MGRT with religious leaders on 13 July 2016. A representative of the National Council of Churches of Singapore (NCCS) was present at the consultation to present and explain its position on MGRT. The Council subsequently submitted a written statement on MGRT to the BAC. On 10 May 2018, the BAC conducted another closed-door consultation on MGRT. At that meeting, Polar Body Transfer (PBT), a relatively new technique used in MGRT, was also discussed. A representative of the Council was also present at that consultation, and its view on PBT was presented and discussed. On 19 April 2018, the BAC published a consultation paper entitled, 'Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology' in which it also states that it is reviewing its current prohibition of germline modification that was presented in its 2005 report.[vi]

This paper is the response of NCCS to the BAC consultation paper on MGRT published on 19 April 2018.

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[i] Gorman et al. 'Prevalence of Nuclear and Mitochondrial DNA Mutations Related to Adult Mitochondrial Disease', *Ann Neural* 77 (2015): 753-759.

[ii] Laura Bainbridge, *Understanding and Coping With Mitochondrial Disease* (Hamilton Health Sciences, 2010), 1.

[iii] A sub-category of mitochondrial disease known as Mitochondrial myopathies includes a group of neuromuscular diseases such as Kearns-Sayre syndrome (KSS), Leigh's syndrome, Mitochondrial Depletion syndrome (MDS), Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like spisodes (MELAS), Myoclinic epilepsy and Ragged Red Fibers (MEERG), Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE), Neuropathy, Ataxia, and Retinis Pigmentosa (NARP), Pearson syndrome, and Chronic Progressive External Opthalmoplegia (CPEO).

[iv] Ibid.

[v] Jalelah Abu Baker, 'Bioethics Committee Reviewing Stand on Genetic Modification for Mitochondrial Disorders', Channel Newsasia, 19 April 2018. https://www.channelnewsasia.com/news/singapore/bioethics-committee-review-genetic-modificationmitochondrial-10152826, accessed.

[vi] Bioethics Advisory Committee, Singapore. Genetic Testing and Genetic Research, November 2005, Recommendation 12.

Annexe C

THEOLOGICAL AND ETHICAL ISSUES

While the Council understands the desire of women with mitochondrial disorders to have genetically related children, it has to assess the MGRT on the basis of broader theological and ethical issues that this technology raises. These issues not only concern the safety of the technology for the people involved in the procedure (the mother and the egg donor) including the offspring. They include much broader concerns like the moral status and dignity of the human embryo and the ethical issues raised by the fact that the creation of the child requires genetic material from three individuals. Theologians and bioethicists are also concerned about the ramifications that MGRT, which is a form of germline modification, would have on the progeny of the child, whose genome has been altered by the mtDNA of the donor.

In this section, these theological and ethical issues are discussed in some detail in the hope that the reasons why the Council must reject MGRT are made clear. Although this paper is written in response to the BAC consultation paper on MGRT, its purpose is also to expound the Council's position on MGRT that its earlier (and significantly briefer) statement has articulated. While the BAC consultation paper discusses the science and ethics of MGRT in some detail, it has omitted some important topics that, in the view of the Council, should be included if the public is to have a fuller understanding of the technology in question. Thus, issues like safety (which is not given enough attention in the BAC paper) and the risks of egg donation (which it totally omits) are discussed in this paper.

The Dignity of the Embryo

One of the main concerns of the Council regarding MGRT is that in various ways the techniques violate the dignity of the embryo. The Council recognises the fact that the idea of human dignity has become contentious in ethical discussion. It works with a very basic theological understanding of dignity premised on the view that human beings are created in the image and likeness of God (Genesis 1:27). The Roman Catholic ethicist William May describes this as the first and basic dignity proper to human beings, a 'dignity that is theirs simply as living members of the human species, which God called into being …' May continues: 'Every human being is a living image of the all-holy God and can therefore rightly be called a "created word" of God, the created word that his Uncreated Word became and is precisely to show how much God loves us'.[vii]

The Council is unable to endorse MGRT because some of the techniques – in particular, pronuclear and blastomere transfer – involve the destruction and construction of the human embryo. Maternal spindle transfer presents other issues surrounding genetic lineage and identity that will be discussed below. The Council takes a very serious view of these procedures because it maintains that human life begins at conception. This means that at the point of conception, the organism of human parentage is already a human being worthy of the respect and protection due to all human beings. Although the Bible does not deal specifically with the question of when human life begins, there are numerous passages that state that the emergence of human life cannot be treated as an arbitrary event (E.g., Jeremiah 1:5). In addition, the Bible makes it clear that God is profoundly interested in the human being and is actively involved in his or her development from the very beginning (E.g., Psalm 139:13-16).

Based on these considerations, the Council maintains that it is theologically and philosophically untenable to distinguish between the pre-embryo and the embryo, or between the zygote that merely possesses human life and the foetus that is a human being. The Council maintains that the view that the zygote must be regarded as a human being from conception is not only theologically warranted; it is also philosophically compelling. At conception, the zygote of human parentage

[vii] William May, *Catholic Bioethics and the Gift of Human Life* (Huntington, Indiana: Our Sunday Visitor, 2000), 53.

is already endowed with its own genetic code and its human nature. It will develop into an adult human being. The zygote of human parentage can never articulate itself into another creature. This is because the human zygote or embryo shares the same nature with its human parents. And although it is true that scientists have not achieved a consensus on this issue about the beginning of human life – which shows that science alone cannot provide us with the definitive statement of what it means to be human – a number of scientists have rejected the artificial distinction between pre-embryo and embryo. For example, in Human Embryology & Teratology, Ronan O'Rahilly and Fabiola Müller argue that:

… although life is a continuous process, fertilisation is a critical landmark because, under ordinary circumstances, a new genetically human organism is thereby formed … The combination of 23 chromosomes present in each pronucleus results in 46 chromosomes in the zygote. Thus, the diploid number is restored and the embryonic genome is formed. The embryo now exists as a genetic unity.[viii]

Consequently, they maintain that 'pre-embryo' is a concept that is 'ill-defined and inaccurate' and list it as one of the 'discarded and replaced terms'.[ix]

In a 2008 White Paper commissioned by The Westchester Institute for Ethics and the Human Person entitled, 'When Does Human Life Begin?' Maureen L. Condic, Associate Professor of Neurobiology and Anatomy at the University of Utah School of Medicine and Senior Fellow of the Institute, argues that from the moment of conception, the zygote is a full human organism that will develop into a mature human adult unless it is impeded by disease or external intervention.

From the moment of sperm-egg fusion, a human zygote acts as a complete whole, with all the parts of the zygote interacting in an orchestrated fashion to generate the structures and relationships required for the zygote to continue developing towards its mature state. Everything the sperm and the egg do prior to their fusion is uniquely ordered towards promoting the binding of these two cells. Everything the zygote does from the point of sperm-egg fusion onward is uniquely ordered to prevent further binding of sperm and to promote the preservation and development of the zygote itself. The zygote acts immediately and decisively to initiate a program of development that will, if uninterrupted by accident, disease or external intervention, proceed seamlessly through formation of the definitive body, birth, childhood, adolescence, maturity, and aging, ending with death. This coordinated behaviour is the very hallmark of the organism.[x]

The zygote therefore cannot be seen merely as a human cell because it is already an individual human being:

Based on a scientific description of fertilization, fusion of sperm and egg in the "moment of conception" generates a new human cell, the zygote, with composition and behaviour distinct from that of either gamete. Moreover, this cell is not merely a unique human cell, but a cell with all the properties of a fully complete (albeit immature) human organism; it is "an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent: a living being".[xi]

If the embryo or zygote is a human being worthy of respect and protection, any attempt to regard it as mere biological material must be rejected because this would violate its inherent dignity. Yet, this is precisely what MGRT does to the human embryo – it reduces it to a mere artefact, biological material that can be assembled, manipulated or destroyed. If the human embryo is indeed worthy

[viii] Ronan O'Rahilly and Fabiola Müller, *Human Embryology & Teratology*. 3rd Edition. (New York: Wiley-Liss, 2001), 8.
[ix] Ibid., 28.
[x] Maureen L. Condic, 'When Does Human Life Begin? A Scientific Perspective', The Westchester Institute for Ethics & the Human Person, White Paper, Volume 1, Number 1, October 2008: 7.
[xi] Ibid.

of respect, no one has the right to destroy one human embryo in order to construct another. The Council therefore rejects the use of these procedures as unethical because they not only result in the destruction of human embryos; they also treat human beings as mere objects that can be fashioned by our technologies. As Agneta Sutton puts it:

Both in the case of pronuclear transfer and in that of blastomere nuclear transfer the resulting aggregate embryos – and hence the children-to-be – are assembled like manufactures. In the case of pronuclear transfer the building material are two sacrificed embryos. In the case of nuclear transfer the building material are embryonic cells and egg cells. In both cases the production of the resulting 'combi-embyro' is totally depersonalising.[xii]

These objections apply to maternal spindle transfer (MST) even though the procedure does not result in the destruction of the embryo. However, it is important to note that although no embryos will be destroyed in the clinical application of MST, this is not the case at this current stage of its development. The studies show that while the techniques have enjoyed some success, there are also very significant failures. For example, while MST has succeeded in producing four live-born monkeys, a significant number of embryos were also damaged or deemed defective in the process, and were therefore unable to develop to maturity. This is reported in two important studies of the result of MST on primates. For example, in their paper titled, 'Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells', Sparman et al. reported that only 46 monkey embryos out of 84 produced by MST were able to develop even to the blastocyst stage (that is, day 5-7 of development).[xiii] Furthermore, according to this report, out of the 15 monkey embryos transferred to the surrogate mother, only four pregnancies resulted. This means that the success of the technique, its ability to produce 'healthy' offspring is dismal because only a small fraction of the embryos originally generated survived. As Maureen L. Condic puts it, this means that 'this procedure was lethal for the great majority of the embryos it produced'.[xiv]

In order to investigate whether this technique will work in human beings, human embryos must be created specifically for the purpose of this research many of which will be destroyed and discarded. As César Palacious-González points out, '… before MST moves into assisted reproduction centres many human embryos will be intentionally destroyed during research'. But even when the technique has achieved a certain level of development and proficiency, embryos will still be intentionally destroyed whenever more research to improve or vary the procedure is conducted. Palacious-González explains:

Furthermore, intentional embryo destruction in the MST context is not limited to the initial developmental phase, but would also occur if and when major changes are introduced in the way in which the technique is carried out. If there were significant improvements or variations to the technique them embryos would also be created and destroyed while researching the safety and efficacy of the modified MST technique.[xv]

The same problem is encountered in studies on Polar Body Transfer (PBT). Because this technique is newer than existing ones like MST and PNT, more studies must be conducted not only to ensure that it is safe but also to probe deeper into the genome of embryos created in order to detect genetic differences and possible pathologies. Based on the current knowledge about the incidence of epigenetic programming errors in somatic cell nuclear transfer, Wei et al. state that 'Whether polar body transfer increases the risk of epigenetic disorders in offspring and subsequent

[xii] Agnetta Sutton, 'The Moral Cost of Techniques for the Prevention of Mitochondrial DNA Disorder', *Catholic Medical Quarterly*, August 2013. http://www.cmq.org.uk/CMQ/2013/Aug/moral_cost_of_preventing_mitocho.html.

[xiii] Tachibana M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, Woodward J, Li Y, Ramsey C, Kolotushkina O, Mitalipov S. 'Mitochondrial gene replacement in primate offspring and embryonic stem cells.' *Nature*, 2009 Sep 17; 461(7262): 367-72.

[xiv] Maureen L. Condic, 'Mitochondrial Donation: Serious Concerns for Science, Safety and Ethics', Science Briefing, February 19, 2015, 5.

[xv] César Palacious-González, 'Are There Moral Differences Between Maternal Spindle Transfer and Pronuclear Transfer?' Medicine, Health Care, and Philosophy 2017, 20(4), 10.

generations requires further investigation. It will be important to study epigenomic patterns of human preimplantation embryos generated by polar body transfer to confirm the consistency of epigenetic models between those generated by polar transfer and normal ones'. Such studies will invariably result in the destruction of human embryos.[xvi]

In addition, the egg and sperm should not be seen as mere human tissue. Their special status must be acknowledged because they not only give rise to life, they are also a means by which the genetic lineage of the child is determined. The same can be said of the mitochondrial genes because they are passed down from generation to generation through the maternal line. When the nDNA of an egg is separated from the egg's mitochondria and replaced with mitochondria from a donor egg to form a new egg, 'the DNA of the resulting egg no longer serves as a true pointer backwards. It is not that it gives a mixed message. It gives a false message'.[xvii]

This leads us to an issue that relates not just to MGRT but also to other forms of assisted reproduction technology (ART), namely, the subtle but significant shift from the language of procreation to reproduction. As Leon Kass has pointed out more than thirty years ago, the shift to a metaphor associated with the factory has profound implications on the way in which we understand what it means to have children.[xviii] Borrowing from the language of the Nicene Creed, the Anglican theologian Oliver O'Donovan reminds us that children are 'begotten, not made'.[xix] The shift from 'procreation' to 'reproduction' – from the metaphor associated with the mutual selfgiving of the husband and wife to that associated with manufacturing or engineering – has profound implications. It introduces, albeit very subtly, the ideas of commodities, the production line, quality control, and the rejection of inferior products to our understanding of having children. By treating the child-to-be as a collage assembled put together by scientists, MRT violates its dignity. As Sutton points out:

The aggregate egg to be fertilised is … effectively a bit of brickwork. And because the 'combi-egg' is a bit of brick-work or an aggregate, so too is the IVF embryo. In this situation too, the end-product, the embryo created as a result of the procedures, is a product of *homo faber*.[xx]

In its written submission after the closed-door consultation conducted by the BAC, the Council states:

MGRT … sits uneasily with our understanding of conventional medicine. The metaphor of healing associated with medicine is replaced with that of engineering associated with manufacture. By treating the child as a construct, such depersonalising technologies change our perception of procreation itself. And this raises profound concerns about the objectification of children.

We can illustrate this by simply asking who is the patient – i.e., who is being treated – in MGRT? In traditional medicine who the patient is is never in question. The same, however, could not be said about MGRT. The patient surely cannot be the mother with a mitochondrial disorder. In the case of PNT, the patient is not the mother's embryo created by IVF because that embryo is destroyed. Nor can we say that the embryo constructed with the mitochondria of the donor is the patient. This is because the 'treatment' was not applied to the embryo itself; neither did it begin after the embryo was brought into being but before its creation. Even in MST and PBT it is not at all clear who the patient is. The IVF embryo is not the patient because it was not itself the recipient of the 'treatment'. In fact, in all three procedures the resulting embryo cannot be said to be the

[xvi] Wei Yanchang, Zhang Teng, Wang Ya-Peng, Schatten Heide nd Sun Qing Yuan, 'Polar Bodies in Assisted Reproductive Technology: Current Progress and Future Perspectives', Biology of Reproduction, Volume 92, Issue 1, 1 January 2015, 19, 5.

[xvii] César Palacious-González, 'Are There Moral Differences Between Maternal Spindle Transfer and Pronuclear Transfer?' Medicine, Health Care, and Philosophy 2017, 20(4), 10.

[xviii] Leon Kass, *Towards a More Natural Science* (New York: The Free Press, 1085), 48.

[xix] Oliver O'Donovan, *Begotten or Made?* (Oxford: Oxford University Press, 1984).

[xx] Agnetta Sutton, 'The Moral Cost of Techniques for the Prevention of Mitochondrial DNA Disorder', *Catholic Medical Quarterly*, August 2013. http://www.cmq.org.uk/CMQ/2013/Aug/moral_cost_of_preventing_mitocho.html

patient, which in medicine traditionally refers to the subject of healing. Agnetta Sutton is therefore right to conclude that:

The ultimate hoped for end-product, the child, might be healthy and it might come to be loved like any other child, but it was not given therapeutic treatment. Mitochondrial replacement technologies are beyond the pale of conventional medicine. What is taking place is best described as a kind of engineering. And as argued, fabrication of embryos by aggregation of embryonic and/or gametal parts is a depersonalising technology. Pronuclear transfer, blastomere nuclear transfer and maternal spindle transfer fail to respect not only the humanity of the human embryo, but also the human dignity of the child or child-to-be. These technologies distort intergenerational relationship inasmuch as nascent human life is treated as mere inanimate matter and the child-to-be as a construct.[xxi]

Three-Parent Babies

In its statement issued in February 2015 in response to the legalisation of MGRT in the UK, the Council made clear that its basic theological objection to the procedure is that it would result in a child with three genetic parents. '[T]he intrusion of a third party in the process of procreation', it states, 'is a serious violation of the structure of the family that God has ordained'.[xxii] This objection is based on the order put in place by the Creator in which sexual relations and procreation must be confined to the covenant of marriage between a man and a woman. Speaking more generally about assisted reproductive technologies involving a third party donor of gametes, Joseph Francis explains: 'God's ideal for the family is participation of both a mother and father in procreation and raising of children. This rules out cloning and most third party, substitute, or donor arrangements'.[xxiii] MGRT, which uses the healthy mitochondria from a donor, violates God's ideal for the family because it creates a child not just with the genetic contributions of the husband and wife but also that of another person outside the marriage.

Some supporters of MGRT have objected to the use of terms such as 'three-parent embryos', 'three-parent babies' and 'three-person IVF'. For example, the Nuffield Council maintains that since the genetic and social parents provide 99.9% of the total genetic material, and since physical as well as the character traits constitutive of identity are coded in the nDNA and not the mtDNA, it is misleading to use these terms to describe babies that are born after MGRT.[xxiv] The UK Department of Health also rejects the view that the child created through MGRT can be said to have three parents:

Genetically, the child will, indeed, have DNA from three individuals but all available scientific evidence indicates that the genes contributing to personal characteristics and traits come solely from the nuclear DNA, which will only come from the proposed child's mother and father. The donated mitochondrial DNA will not affect those characteristics.[xxv]

This view is echoed by the UK public, according to the major study by the Human Fertilisation and Embryology Authority published in 2013. 'Most rejected the 'three parent IVF' idea, arguing that mitochondrial DNA contributes little or nothing to a child's personal characteristics and the donor should not therefore be regarded as a parent', HFEA reports.[xxvi] When asked about their

[xxi] Agnetta Sutton, 'The Moral Cost of Techniques for the Prevention of Mitochondrial DNA Disorder', *Catholic Medical Quarterly*, August 2013. http://www.cmq.org.uk/CMQ/2013/Aug/moral_cost_of_preventing_mitocho.html.

[xxii] Mitochondrial Replacement Technologies: A Statement by the National Council of Churches in Singapore', http://ethosinstitute.sg/wp-content/uploads/2015/01/Mitochondrial-Replacement-Technology.pdf.

[xxiii] Joseph Francis, 'The Christian and Assisted Procreation', *The Baptist Bulletin*, January 2000, 7.

[xxiv] Nuffield Council on Bioethics, 2012. Novel Techniques for the Prevention of Mitochondrial DNA Disease: An Ethical Review. Available from: http://www.nuffieldbioethics.org/sites/default/files/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_diseases_compressed.pdf/.

[xxv] Department of Health. 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 22 July 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/ file/332881/Consultation_response.pdf (accessed on 21 March 2015).

[xxvi] Human Fertilisation and Embryology Authority, *Mitochondrial Replacement Consultation: Advice to Government* (March 2013), 21. Available at http://www.hfea.gov.uk/docs/Mitochondria_replacement_consultation_-_advice_for_Government.pdf.

initial reaction to the procedure, 44% said they were 'very' or 'fairly' positive and only 15% were 'very' or 'fairly' negative.[xxvii]

At the July 13, 2016, BAC consultation meeting, two members of the BAC questioned the propriety of describing the baby created by MGRT as having 'three parents'. In its 19 April 2018 consultation paper, the BAC admits that 'a child born of MGRT will inherit genetic material from three parents' but pointed out that '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' (p. 23). However, it must be pointed out that the fact that the egg provider contributes only 0.1% of the total genetic make-up through her healthy mtDNA does not mean that it is inaccurate to postulate that babies created by MGRT have three genetic parents. The percentage of the contribution by the third party is irrelevant. As Françoise Baylis has rightly pointed out, 'All that is relevant to this issue is the presence or absence of identifiable genetic material from someone other than the two individuals identified as the genetic parents'.[xxviii] Only when the egg donor is a close maternal relative of the woman who is the genetic parent would their mitochondrial be identical, since mtDNA passes through the female line. But as MGRT is purposed to prevent the transmission of diseases caused by mutations in the mtDNA, it is unlikely that the egg donor would be a close relative. 'If the egg provider is not a close relative', Baylis rightly argues, 'then there would be identifiable genetic material from a second female genetic parent, in which case any child born following the mitochondrial replacement would have three genetic parents'.[xxix] Here, the Council must clarify that even if perchance the mitochondrial donor is a close relative of the mother, by virtue of her donation she has already violated the structure of the family that is ordained by God. Put differently, even if the donor belongs to the same haplogroup as the mother, her involvement itself must still be seen as a third-party intrusion to the procreative process that must be confined to the husband and the wife who are joined together in the covenant of marriage. In addition, as Cohen and Alikan have argued, even though physical and personal traits come from the nuclear DNA and not the mtDNA, from the standpoint of biology all babies born through MGRT must still be considered as tri-parental.[xxx]

We return to the argument made by the Nuffield Council that because it is the nDNA that provides character traits and not the mtDNA, the contribution of the third party in MGRT is inconsequential to the identity of the child. This argument is premised on a very narrow view of identity. Françoise Baylis is right to point out that 'identity is not in the genes but in the world in which we live and the stories we construct and are able to maintain'.[xxxi] Developing this relational account of identity, Baylis adds: '[A] person's identity (including her traits, desires, beliefs, values, emotions, intentions, memories, actions and experiences) is informed by her personal relationships – relationships characterised by degrees and kinds of intimacy and interdependence'.[xxxii] This means that the state of health of the individual influences and shapes his or her identity in profound ways. A child who is spared of mitochondrial disease as a result of MGRT would develop very differently from a child who has the disease because her mother did not undergo the procedure. This means MGRT can be said to have an impact on the child's identity. As Baylis explains:

Viewed from this perspective, health and illness are states of being that very much inform personal identity and it makes no sense to say that a safe and effective technology that eliminates mitochondrial disease in the newborn will have no impact on how the person's identity evolves.[xxxiii]

[xxvii] Ibid.

[xxviii] Françoise Baylis, 'The Ethics of Creating Children with Three Genetic Parents', Reproductive Biomedicine Online (2013), 26, 532. Available at http://www.rbmojournal.com/article/S1472-6483(13)00132-6/fulltext?mobileUi=0.

[xxix] Ibid.

[xxx] Cohen J, Alikani M. 'The Biological Basis for Defining Bi-parental or Tri-parental origin of Offspring from Cyto-plasmic and Spindle Transfer'. Reprod Biomed Online 2013; 26:535–7.

[xxxi] Fransçoise Baylis, 'Black as Me: Narrative Identity', Developing World Bioethics 3, 2003, 142.

[xxxii] Fransçoise Baylis, 'The Self In Situ: A Relational Account of Personal Identity'. In J. Downie and L. Llewellyn (Eds.), *Relational Theory and Health Law and Policy* (Vancouver: UBC Press, 2011), 109.

[xxxiii] Françoise Baylis, 'The Ethics of Creating Children with Three Genetic Parents', Reproductive Biomedicine Online (2013), 26, 532. Available

'It follows', Baylis concludes, 'that a third-party genetic contribution of healthy mtDNA is important in shaping a person's narrative, viz. determining who a person will be'.[xxxiv]

Turning to the legal aspects of MGRT especially with regard to legal maternity, the BAC points out that '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) that the gestational mother is treated as the legal mother, while egg and sperm donors are not treated as parents' (p. 23). While the law here is clear at this point in time, as ART becomes more prevalent and as the demand for surrogate motherhood becomes more pressing,[xxxv] the definition of legal parentage may change. Many scholars have predicted that parentage disputes will arise in the age of MGRT, and views about the parentage rights of the mitochondrial donor will be revised. For instance, some have argued that parentage disputes in the context of MGRT should be resolved in the same way as parentage disputes in the context of gametes donation: by applying the intent test. 'Although a mitochondrial donor contributes less than 0.001% of her DNA', writes Amy Leiser, 'her legal claim for parentage rights, if she is an intentional lender of procreative genetic material, should be equally as strong as any other claim by an intentional lender of procreative material because she had the requisite intent and her donation was procreative'.[xxxvi] In what sense is her donation procreative? Leiser explains: 'Where the other intending mother is infertile or carries a mitochondrial disease, the mitochondrial donation is procreative because conception of a healthy child is impossible without the egg donor'. She concludes: 'Therefore, when the mitochondrial donor is actually an intentional lender of procreative genetic material, she should have a claim to legal parentage rights equal to that of any other intending parent'.[xxxvii]

MGRT As Germline Modification

The question that must be given serious consideration is whether MGRT is a form of germline modification. This question is important because most countries have currently imposed a moratorium on germline modification procedures because of the unascertainable risks they may pose to future generations. International bodies like the Council of Europe, for example, have categorically prohibited human germline modification. Article 13 of the Council of Europe's 1997 document on the protection of human rights and dignity states 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'.[xxxviii] The BAC paper has noted these international regulations on germline modification (pp. 14-15). In an article entitled, 'Which Ills to Bear', Alexander Capon explains why germline modification should be distinguished from other forms of therapy, including somatic cell therapy, thus:

The major reasons for drawing a line between somatic-cell and germ-line interventions … are that germ-line changes not only run the risk of perpetuating any errors made into future generations of non-consenting 'subjects' but also go beyond ordinary medicine and interfere with human evolution. Again, it must be admitted that all medicine obstructs evolution. But that is inadvertent, whereas with human germ-line genetic engineering, the interference is intentional.[xxxix]

The Council likewise maintains that any kind of inheritable genetic modification that will affect future generations must be prohibited. It fully agrees with the position of the Roman Catholic

at http://www.rbmojournal.com/article/S1472-6483(13)00132-6/fulltext?mobileUi=0.

[xxxiv] Ibid.

[xxxv] Amy M. Lardy, 'Redefining Motherhood: Determining Legal Maternity in Gestational Surrogacy Arrangements', Drake Law Review, Volume 51, No. 3, 12003: 605-632.

[xxxvi] Amy Leiser, 'Parentage Disputes in the Age of Mitochondrial Replacement Therapy', 431, http://georgetownlawjournal.org/files/2016/01/Leiser-ParentageDisputesintheAgeofMitochondrialReplacementTherapy.pdf (accessed May 2016).

[xxxvii] Ibid.

[xxxviii] Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* Orvieto: 1997. ETS no 164.

[xxxix] Alexander Capon, 'Which Ills to Bear: Reevaluating the 'Threat' of Modern Genetics', *Emory Law Journal* 1999, 29: 676.

Church that is clearly articulated in *Dignitas Personae*:

The moral evaluation of germ line cell therapy is different. Whatever genetic modifications are effected on the germ cells of a person will be transmitted to any potential offspring. Because the risks connected to any genetic manipulation are considerable and as yet not fully controllable, in the present state of research, it is not morally permissible to act in a way that may cause possible harm to the resulting progeny. In the hypothesis of gene therapy on the embryo, it needs to be added that this only takes place in the context of in vitro fertilization and thus runs up against all the ethical objections to such procedures. For these reasons, therefore, it must be stated that, in its current state, germ line cell therapy in all its forms is morally illicit.[xl]

The Council, however, recognises that the question whether MGRT is a form of germline modification is a contentious one. There is no consensus to date among scientists and ethicists, although some key distinctions have been identified and underscored. Firstly, it has been pointed out that MGRT concerns only mtDNA while, generally speaking, germline therapies target the nDNA. This distinction is emphasised in some policy reports like the 2014 Public Health Directorate, which acknowledges that MGRT has germline implications but rejects that it is a form of 'genetic modification' because the latter has to do with heritable modifications of only nDNA.[xli] As we shall see, distinction between mtDNA and nDNA is of dubious significance in ethics, and should therefore be called to question. Secondly, the transplanted mitochondrial is heritable only in the maternal line and therefore does not affect the male offspring. This has been described as the 'quasi-inheritability' of MGRT. For these reasons, some scientists and researchers have concluded that MGRT is not a form of germline modification because it targets only the mtDNA.[xlii]

In response, the Council would like to point out that nomenclatures for emerging and new biotechnologies are sometimes coined in a notoriously haphazard fashion.[xliii] Once chosen, however, the nomenclature has the ability to introduce enduring perceptions and connotations, some of which can be dangerously misleading. The misconceptions they engender are significant because they often influence ethical and policy debates. Mitochondrial transfer technologies have been known by many names: 'mitochondrial donation', 'mitochondrial replacement', 'mitochondrial therapy' and 'mitochondrial transfer'. Perhaps the most accurate descriptor is 'mitochondrial transfer'. Furthermore, it is not at all difficult to see how some descriptors may mislead the public concerning what MGRT is about and what it aims to achieve. Whether MGRT is considered to be a form of germline modification very much depends on how one defines germline modification. For example, the NASEM report makes the distinction between 'genetic modification' and 'germline modification'. It argues subsequently that 'MRT involves genetic modification, but that it constitutes … germline modification … only if used to produce female offspring'.[xliv] But even here, NASEM admits that MRT must be regarded as germline modification, albeit under certain circumstances.

Despite the current lack of consensus, the Council maintains that MGRT is a form of germline modification. The view of the Council is shared by a number of scientists working in the field.[xlv] Writing just before the UK decision to trial MGRT, Marcy Darnovsky, Executive Director of the

[xl] *Instruction* Dignitas Personae *On Certain Bioethical Questions,* http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_20081208_dig nitas-personae_en.html, accessed 24 April 2015.

[xli] See Public Health Directorate/Health Science and Bioethics Division (2014) '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'. London: Department of Health.

[xlii] See, for example, North East England Stem Cell Institute (NESCI). (2008). http://www.ncl.ac.uk/nesci/research/legal/embryonic/documents/NESCIbriefon2008HFEbill-MitochondrialTransplants-Vers01-6.pdf.

[xliii] Ainsley J Newton, Stephen Wilkinson and Anthony Wigley, 'Ethical and Legal Issues in Mitochondrial Transfer', *EMBO Molecular Medicine,* Vol. 8, No. 6, 2016, 589.

[xliv] National Academies of Sciences Engineering and Medicine (NASEM) (2016) Mitochondrial Replacement Techniques: ethical, Social, and Policy Considerations. Washington DC: The National Academies Press, Section 3, 8.

[xlv] See Bredenoord, A.L., et al. (2008). Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues. *Human Reproduction Update,* 14(6), 669-678 and Robertson, J.A. (1998). 'Oocyte cytoplasm transfers and the ethics of germ-line intervention'. *Journal of Law, Medicine, and Ethics* 26, 211-220.

Annexe C

Centre for Genetics and Society in Berkeley, California, asserts:

Mitochondrial-replacement procedures would constitute germline modification. Were the United Kingdom to grant regulatory go-ahead, it would unilaterally cross the legal and ethical line on this issue that has been observed by the entire international community. This consensus holds that genetic-engineering tools may be applied, with appropriate care and safeguards, to treat an individual's medical condition, but should not be used to modify gametes or early embryos and so manipulate the characteristics of future children.[xlvi]

Supporters of MGRT have argued that this procedure should not be regarded as germline modification because only nDNA influences inheritable character traits, while mtDNA does not. Some countries, like the Netherlands, have made the distinction between nDNA and mtDNA the basis for legalising certain procedures. Thus, in the Dutch Embryo Act (2002), modifying the mtDNA is legally permissible while modifying the nDNA is strictly prohibited. While the BAC agrees that MGRT is a type of germline modification, it maintains that it is different with other forms of germline modification the targets the nuclear genome because it only replaces the mitochondrial genome. 'Since the mitochondrial genome comprises much fewer genes', it argues, 'the scope of functional changes that MGRT could introduce is relatively limited' (p. 25).

The Council questions the tenability of this strict dichotomy between nDNA and mtDNA. Bredenoord et al. have pointed out that such dichotomies are misleading because much 'is unknown about nucleo-mitochondrial interaction'.[xlvii] Darnovsky concurs. In an article that was cited above, she writes: 'Supporters argue that these concerns do not apply to modifications of mitochondrial DNA, which they characterise as an insignificant part of the human genome that does not affect a person's identity. This is scientifically dubious. The genes involved have pervasive effects on development and metabolism'.[xlviii]

The fact is that too little is known about the role and function of mtDNA to confidently conclude that it makes absolutely no contribution to the phenotype. In fact, there are a number of studies that seem to indicate that mtDNA has a more profound function than just governing cellular energy production. For example, in one study the possible link between mtDNA and cognitive functioning in mice is established.[xlix] Another study detects a possible connection between mtDNA variation and susceptibility to alcoholism.[l] Commentators like I. Szebik have warned against too hastily jumping to the conclusion that mtDNA makes no contribution whatsoever to individuality, and that it is therefore ethically irrelevant. Since mtDNA influences the function of the mitochondria, which in turn influences energy production of neural cells, it may have a greater impact on individuality than hitherto envisaged.[li] In their article entitled, 'Inadvertently Crossing the Germ Line', S. Parens and E. Juengst note that mtDNA is often not taken seriously in ethical and policy debates on genetic engineering 'on the basis of the weak assumption that it does not have significant phenotypic effects'. However, they caution against such an approach because 'mitochondria do govern cellular energy production, and we are learning more about the downstream and far-reaching effects of that function on human physiology and (through the brain) on human behaviour'.[lii] These researches show that there is much we have yet to discover about the function of mtDNA. The Council maintains that for this reason, and also because ongoing research is revealing more about the downstream effects of mitochondria, MGRT, as a form of germline modification, should be prohibited.

[xlvi] Marcy Darnovsky, 'A Slippery Slope to Human Germline Modification', Nature, 9 July 2013.

[xlvii] A.L. Bredenoord, G. Pennings, and G. de Wert ,'Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues', Hum. Reprod. Update (2008) 14 (6): 670.

[xlviii] Darnovsky, 'A Slippery Slope to Human Germline Modification'.

[xlix] Roubertoux PL, Sluyter F, Carlier M, Marcet B, Maarouf-Veray F, Chérif C, Marican C, Arrechi P, Godin F, Jamon M, et al. 'Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice'. Nature Genet 2003;35:65-69.

[l] Lease LR, Winnier DA, Williams JT, Dyer TD, Almasy L, Mahaney MC. 'Mitochondrial genetic effects on latent class variables associated with susceptibility to alcoholism'. *BMC Genet* 2005;6 Suppl I:S158.

[li] Szebik I. 'Response to 'Germ Line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation' by Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, Michael J. Zinaman; *Cambridge Q Healthc Ethics*. Vol. 8. 1999.p. 369-374.

[lii] Parens E, Juengst E. 'Inadvertently Crossing the Germ-line'. *Science* 2001;292:397.

We turn our attention now to address, albeit very briefly, the issue of slippery slope arguments (SSAs) discussed in the BAC paper (p. 25). The first point to be made is that SSAs must be taken very seriously in bioethics, especially if the abuses and excesses they warn about present themselves as reasonable, possible and probable. SSAs play a significant role in discourse in other fields, for example, legal debates.[liii] In addition, if SSAs are used even in debates on older issues in bioethics like physician-assisted suicides and euthanasia,[liv] why should they not be used in discussing the ethics of 'frontier biotechnologies', such as MGRT, germline modification technology and gene editing? In fact, bioethicists are going beyond SSAs and employing fiction (especially science fiction) to help them to imagine possible futures based on the potentialities of existing technologies, and to envision plausible scenarios – utopias or dystopias (mostly dystopias!).[lv]

The legalisation of MGRT could leave the door ajar for the legalisation of more forms of germline gene modification on which there is a moratorium in many countries (the fact that the BAC is presently conducting a study on the feasibility of legalising germline modification in Singapore is a case in point!), and the non-therapeutic use of the technology. As Tetsuya Ishii postulates:

Legalization in the UK might cause another slide down the slippery slope to full-blown germline gene modification because the slope to further genetic modification will seem less steep than is the case with the current total ban.

Present-day genome-editing technology, such as that now offered by zinc finger nuclease, transcription activator-like effector nuclease and clustered regularly interspaced short palindromic repeat (CRISPR)/Cas technologies, has demonstrated highly specific and efficient nuclear genome engineering in human cells. Human T cells modified with the artificial nuclease have already been used in a clinical trial of AIDS therapy in the USA. A simple injection of CRISPR/Cas mRNA into zygotes can modify target genes in the genome, resulting in genetically modified monkeys. Some researchers would advocate that genome editing is appropriate to germline gene therapy if it may repair a mutated gene without off- target mutations.

Furthermore, some people might use the state-of-the- art genetic engineering for enhancement.[lvi]

It is difficult not to take such SSAs seriously.

Safety Concerns

One of the major concerns associated with MGRT is the safety of the technique. Can we be sure that the technique that aims to free the child from mitochondrial disease will not cause other harms to it? Can we be sure that this technique will not harm future generations? While the BAC paper describes the different procedures in some detail, very little is said about their safety and success rates. However, safety is of paramount importance to ethics, especially in artificial reproductive technologies (ART) including MGRT. This concern is clearly articulated in the Human Assisted Reproductive Technology Act of New Zealand published in 2004. It states that 'the health and

[liii] *See, e.g.*, John D. Arras, *The Right to Die on the Slippery Slope,* 8 Soc. THEORY & PRAC. 285, 287-88 (1982) (suggesting that SSAs have become the most common form of argument against legalizing active voluntary euthanasia); Nils Holtug, *Human Gene Therapy: Down the Slippery Slope?,* 7 BIOETHICS 402, 402 (1993) ('I think that many of the worries a lot of us intuitively have concerning gene therapy in fact are worries about a slippery slope ....'); David Resnik, *Debunking the Slippery Slope ArgumentAgainst Human Germ-Line Gene Therapy,* 19 J. MED. & PHIL. 23, 23 (1994) ("One of the more influential arguments against human germ-line gene therapy.., is that it would lead us down a slippery slope ....").

[liv] *See, e.g.*, Krischer v. McIver, 697 So. 2d 97, 109 (Fla. 1997) (Harding, J., concurring); Richard Doerflinger, *Assisted Suicide: Pro-Choice or Anti-Life?* Hastings Centre Report, Jan.-Feb. 1989; Yale Kamisar, *Against Assisted Suicide-Even a Very Limited Form*, 72 *U. Det. Mercy L. Rev.* 735, 741, 749-53 (1994); Yale Kamisar, 'Physician-Assisted-Suicide: The Last Bridge to Active Voluntary Euthanasia', *in Euthanasia Examined: Ethical, Clinical and Legal Perspective*, (ed) John Koewn (Cambridge: CUP, 1995), 225, 245.

[lv] See Nida Nermin YazÕcÕ, Melek AltÕparmakb. 'Science Fiction Aided Biotechnology Instruction: Effects of Bioethics Group Discussions on Achievements and Attitudes', *Porcedia Social and Behavioural Sciences* 2 (2010), 4125-4129 and Sarah Chan, 'More Than Cautionary Tales: The Role of Fiction in Bioethics', *J Med Ethics*, 2009, Jul 35(7): 398-399.

[lvi] Tesuya Ishii, 'Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification', Reproductive Medicine Online (2014) 29, 150-155.

well-being of children born as a result of the performance of an assisted reproductive procedure or an established procedure should be an important consideration in all decisions of the procedure'. It adds further that 'the human health, safety, and dignity of present and future generations should be preserved and promoted'.[lvii] Safety concerns must be emphasised especially when considering new and experimental techniques like MGRT because it is only when the possible harms associated with the technique are well established will we be in the position to assess whether its use is ethical.

The first set of safety concerns has to do with the possible physical harm the procedure could cause the resulting child. The fact that the MGRT-conceived child has three genetic contributors may already pose some serious risk to its wellbeing. One possible risk is that the donor's healthy mtDNA fails to work well with the nuclear DNA of the intending mother.[lviii] Some bioethicists have voiced concern that there might be adverse reactions between the intending mother's nDNA and the donor's mtDNA. For example, there can be a mismatch between the mtDNA haplotype of the mitochondria donor and that of the intending mother that can potentially cause great harm to the MGRT-conceived child.[lix] The child might also develop serious health problems if the donor's mtDNA is incompatible with the nDNA of the intending parent.

Another possible safety issue is that during PNT or MST, some of the diseased mitochondria could be inadvertently transferred to healthy embryo or egg. Some have argued that even if this were to happen, the amount of the diseased mitochondria transferred will be so small that it would be inconsequential. However, as John Appleby has rightly warned: 'While the presence of a very small amount of diseased mtDNA may not be a health risk for the carrier, it could pose a health risk (i.e., a mtDNA disease) for that carrier's offspring'.[lx] As we have seen, while scientists have some knowledge about the nature and function of mitochondria, there is still much that they do not know.[lxi] The hiatus of knowledge of basic mitochondrial biology and genetics suggests that there might be other risks surrounding MGRT for the offspring that we are unable to anticipate at this point.

The BAC paper also discussed a new technique called Polar Body Transfer (PBT) and presented it as a possibly safer alternative to PNT and MST. There are two types of PBT. In PB1T, the nDNA of the donor's unfertilised egg is replaced with the first polar body from the potential mother's unfertilised egg. And in PB2T, the maternal pronuclear DNA of the donor's fertilised egg is replaced with the potential mother's fertilised egg. Drawing from the research of Wang et al.[lxii] the BAC maintains that PBT promises to have an advantage over MST and PNT because it 'reduces abnormal mtDNA carry-over to the child as the polar body contains very little cytoplasm and therefore few cellular organelles such as mitochondria'.[lxiii]

While PBT can in some ways circumvent the transference of abnormal mtDNA to the child, the technique also poses other challenges and risks. In their paper entitled, 'Polar Bodies in Assisted Reproductive Technology: Current Progress and Future Perspective', Wei et al.[lxiv] present the following challenges and risks associated with PBT. Firstly, they note that because the mitochondrial gene pool is shaped through the female germline, the maternal inheritance of mitochondrial is a

[lvii] Human Assisted Reproductive Technology Act 2004, Section 4 a and b. http://www.legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319248.

[lviii] Knoepfler, P. 2014. Open letter to UK parliament: Avoid historic mistake on rushing human genetic modification. BioNews 781. http://www.bionews.org.uk/page_472759.asp. Accessed 26 Nov 2014.

[lix] K Reinhardt, D.K. Dowling, E.H. Morrow. 'Mitochondrial Replacement, Evolution, and the Clinic'. *Science* 2013; 341: 1345–6.

[lx] John B. Appleby, 'The Ethical Challenges of the Clinical Introduction of Mitochondrial Replacement Techniques', *Medical Health Care and Philosophy* (2015), 18: 506.

[lxi] For instance, scientists have insufficient knowledge about the relationship between mitochondria and cancer. See Douglas Wallace, 'Mitochondria and Cancer'. *National Review of Cancer* (2012), 12(10): 685-698. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4371788/. Accessed 14 July 2016.

[lxii] Wang Tian, Sha Hongying, Ji Dongmen, Helen Zhang, Chen Daiwei, Cao Yunxia, and Zhu Jianhong, 'Polar Body Genome Transfer for Preventing the Transmission of Inherited Mitochondrial Diseases', *Cell* 157, June 19, 2014, 1591-1606.

[lxiii] BAC Consultation Paper 2018.

[lxiv] Wei Yanchang, Zhang Teng, Wang Ya-Peng, Schatten Heide nd Sun Qing Yuan, 'Polar Bodies in Assisted Reproductive Technology: Current Progress and Future Perspectives', *Biology of Reproduction*, Volume 92, Issue 1, 1 January 2015, 19, 4.

form of natural selection. Polar body transfer, they maintain, disrupts this process thereby changing the mitochondrial gene pool of humans. Since mitochondrial replacement is a form of germline modification, these changes can be inherited by future generations affecting them in ways that we do not at this point comprehend.

Secondly, citing the paper by K. Reinhart et al.[lxv] they point out that interactions between mitochondrial and nuclear genome are highly specific and coordinated during evolution. Mitochondrial replacement could disrupt this interaction because of the incompatibility between unmatched nuclear and mitochondrial genomes. In addition, studies have shown that there are the risks associated with producing babies in vitro that also needs to be taken into consideration. There is significant data that shows that children produced through ART are at risk of developing serious medical conditions. These include neurological disorders,[lxvi] cancer,[lxvii] and congenital abnormalities.[lxviii] To add to these the possible risk of imprinting disorders and complications resulting from mtDNA-nDNA incompatibility brought about by MGRT is medically irresponsible [lxix]and ethically questionable.

And finally, they maintain that polar PBT may result in epigenetic alterations in the offspring and also in future generations. Based on the known fact that somatic cell transfer has resulted in epigenetic reprogramming errors, Wei et al. state that Whether polar body transfer increases the risk of epigenetic disorders in offspring and subsequent generations requires further investigation. It will be important to study epigenomic patterns of human preimplantation embryos generated by polar body transfer to confirm the consistency of epigenetic models between those generated by polar body transfer and normal ones. It will also be helpful to analyse epigenetic profiling in different tissues of offspring derived from polar transfer.[lxx]

Some have asserted that MGRT is not germline therapy because it only uses the mtDNA of the donor. As we have seen, this is inaccurate. MGRT is a form of germline therapy because it introduces genetic material that would not only alter the genetic make-up of the child produced but also that of subsequent generations along the maternal line. As there is no failsafe way of ensuring the safety of future generations, there is also no way to anticipate the harm that it will cause. The Executive Director of the Center for Genetics and Society, Marcy Darnovsky, is right to observe that 'Unlike experimental gene therapies where risks are taken by consenting individuals, [MGRT] turns children into our biological experiments, and forever alters the human germline in unknowable ways. There is no precedent for this'.[lxxi] Ethicists are also worried that this technique will open the door to other forms of germline modifications on humans whose consequences we are unable to foresee.[lxxii]

[lxv] K Reinhardt, D.K. Dowling, E.H. Morrow. 'Mitochondrial Replacement, Evolution, and the Clinic'. *Science* 2013; 341: 1345–6.

[lxvi] See Hvidtjørn D, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. 'Cerebral Palsy, Autism Spectrum Disorders, and Developmental Delay in Children Born After Assisted Conception: A Systematic Review and Meta-analysis'. Arch Pediatr Adolesc Med. 2009 Jan;163(1):72-83; Kissin DM, Zhang Y, Boulet SL, Fountain C, Bearman P, Schieve L, Yeargin-Allsopp M, Jamieson DJ 'Association of Assisted Reproductive Technology (ART) Treatment and Parental Infertility Diagnosis with Autism in ART-conceived Children'. Hum Reprod. 2015 Feb;30(2):454-65.

[lxvii] Petridou ET, Sergentanis TN, Panagopoulou P, Moschovi M, Polychronopoulou S, Baka M, Pourtsidis A, Athanassiadou F, Kalmanti M, Sidi V, Dessypris N, Frangakis C, Matsoukis IL, Stefanadis C, Skalkidou A, Stephansson O, Adami HO, Kieler H. Pediatr 'In vitro Fertilization and Risk of Childhood Leukemia in Greece and Sweden'., *Blood Cancer*. 2012 Jun;58(6):930-6.; Moll AC, Imhof SM, Cruysberg JR, Schoutenvan Meeteren AY, Boers M, van Leeuwen FE. 'Incidence of Retinoblastoma in Children Born After In-vitro Fertilisation', *Lancet*. 2003 Jan 25;361(9354):309-10.

[lxviii] Olson CK, Keppler-Noreuil KM, Romitti PA, Budelier WT, Ryan G, Sparks AE, Van Voorhis BJ. 'In Vitro Fertilization Is Associated With an Increase in Major Birth Defects'. *Fertil Steril*. 2005 Nov; 84(5):1308-15.; Buckett WM, Chian RC, Holzer H, Dean N, Usher R, Tan SL, 'Obstetric Outcomes and Congenital Abnormalities After In Vitro Maturation, In Vitro Fertilization, and Intracytoplasmic Sperm Injection'. *Obstet Gynecol.* 2007 Oct;110(4):885-91.

[lxix] Maureen L. Condic, 'Mitochondrial Donation: Serious Concerns for Science, Safety and Ethics', Science Briefing, February 19, 2015, 8.

[lxx] Wei Yanchang, Zhang Teng, Wang Ya-Peng, Schatten Heide nd Sun Qing Yuan, 'Polar Bodies in Assisted Reproductive Technology: Current Progress and Future Perspectives', Biology of Reproduction, Volume 92, Issue 1, 1 January 2015, 19, 5.

[lxxi] G. Vogel, 'Mitochondrial Gene Therapy Passes Final U.K. Vote', *Science Insider*, 24 February 2015.

[lxxii] Daniel Eckler, 'Ethics of IVF and MART' in Daniela Barbery, et al, *Should the U.S. Approve Mitochondrial Replacement Therapy?* April 2015, 63.

Annexe C

Given the safety concerns surrounding the procedure (to the woman, the egg donor, the child and the future generation), the low incidence of mitochondrial disease in the population, and the alternatives available for women with mitochondrial disorders,[lxxiii] the clinical use of MGRT is not only medically irresponsible but ethically problematic.

Autonomy and Responsibility

In its consultation paper, the BAC maintains that having genetically related children has to do with personal reproductive 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 persons warrants respect for their reproductive decisions' (p. 18-19). Procreative liberty and reproductive rights are topics that have been the subject of extensive debate in recent years. The Christian faith sees procreation as the outworking of the grace of God in the lives of the husband and wife who through the covenant of marriage have become one flesh (Genesis 2:24). There is an intrinsic link between marriage and procreation. It is only within this context that the Christian can speak of the procreative rights or liberties of individuals, which must always be understood alongside duties and obligations to the offspring whom God has given to them and placed under their care. In addition, the duty and obligation of individuals must extend beyond their immediate children to include future generations insofar as it is within their powers to enable them to flourish and protect them from harm. Seen in this way, the exercise of personal reproductive autonomy from the Christian standpoint must take into consideration wider issues associated with duties and obligations that in some sense also constrain and define such liberties.

The Christian understanding of procreative liberties or rights therefore distinguishes itself from secular accounts in significant ways. Procreation, in the Christian perspective, is inherently relational, not just with respect to the physical bond between parent and child, but also with regard to the parent's moral commitment to the child. Thus, according to the Christian faith, to procreate is not just to exercise one's natural right but also to embrace a sacred duty, that is, to act responsibly to one's offspring, which means, above all, respecting the latter's inherent dignity. As Maura Ryan puts it:

To reproduce is to incur obligations to act so as to protect the conditions for human flourishing on behalf of the one who has come into your care. Reproductive liberty, therefore, presupposes both the willingness and the ability to provide for the physical, social and spiritual needs of the offspring. It also presupposes obligations to respect the equal rights of the offspring, such as the right to respect his or her fundamental uniqueness.[lxxiv]

Because MGRT is a form of germline modification that will introduce irreversible changes to the genetic makeup of the offspring, the duty and obligations of the parents are made significantly more complex. Questions have to be raised concerning the health and safety of the offspring and its inherent rights. Questions also have to be raised about the genetic destinies of the offspring's progeny. To allow the use of a technology that presents serious risks to future generations just so that we may honour the reproductive rights of individuals to have genetically related children is morally irresponsible. Part of the problem with such an approach is the liberal-rights paradigm that bioethics sometimes accept without criticism. To think more responsibly about reproductive rights vis-à-vis duties and obligations is to recognise the limits of the liberal-rights paradigm with

[lxxiii] In its consultation paper, the BAC lists four options currently available to women with mitochondrial disorders: (1) Adoption; (2) In vitro fertilisation (IVF) using healthy donor egg; (3) Pre-implantation Genetic Diagnosis (PGD) and (4) Prenatal Diagnosis. Of these four options, the Council can only endorse adoption. This is because option (2) requires the use of a third party gamete, and options (3) and (4) presents abortion as an option should the diagnosis prove unfavourable. For the Council's position on genetic testing, please see its response to the BAC's 2005 consultation paper on genetic testing and genetic research: http://www.bioethics-singapore.org/index/publications/reports/171-genetic-testing-and-genetic-research.html.

[lxxiv] Maura Ryan, Ethics and Economy of Assisted Reproduction: The Cost of Longing (Washington D.C.: Georgetown University Press, 2001), 111.

its distorting focus on the rights of the individual and to adopt a more social conception of rights, and indeed a more relational understanding of reproduction. As Ryan perceptively points out: 'The failure of reproductive rights talk to generate a satisfying ethic for assisted reproduction points to the importance of shifting from an individual to a relational and social understanding of reproduction and shifting from a view of rights as claims against a community to a view of rights as 'mutual accountabilities''.[lxxv]

We turn now more specifically to the question concerning the kind of moral responsibilities we are required to exercise towards future generations. During its consultation with religious leaders held in July 2016, the BAC poses this question: 'What are your views on the welfare of future generations in the context of clinical trials involving MGRT? Whose interests should we give precedence to – future generations or existing individuals?' The BAC discusses this issue at length in its consultation paper (p. 25). At the outset, we wish to point out that putting the matter in this way creates false alternatives that may cloud our moral judgement. This approach may tempt us to kick the proverbial can down the road, so to speak – that is, to privilege present problems and anxieties and regard problems that might arise in the future as being of secondary importance. However, the welfare of future generations is of paramount importance and any clinical application of a technique or procedure must be made with a profound sense of responsibility that must extend beyond its immediate beneficiaries. Thus, the assumptions of this question must be challenged because to show precedence either to existing individuals or future individuals, that is, to privilege one over the other is in some sense already to act irresponsibly.

The Council maintains that both current and future risks posed by MGRT must be taken seriously – they should not be ignored, neither should one be prioritised over the other. As we have seen from the discussion above, while MGRT may allow individuals to fulfil their desire to have genetically related children, it presents serious risks not only to the immediate offspring, but also to their progeny. In the previous section, we discussed some of the known risks associated with MGRT. We also saw that it is quite possible that there may be other serious consequences for altering the genome of the mitochondria that we are unable presently to anticipate because of our limited knowledge. Commenting on the UK decision to legalise MGRT, Françoise Baylis writes:

The proponents of mitochondrial replacement technology are quick to downplay the potential for harm to offspring born following mtDNA replacement. They insist that there is no evidence the technology is unsafe. The fact is we don't know, and can't know if the technology is safe (and effective) without investing considerable time, talent and money in research to investigate the potential short- and long-term harms to both the offspring and their progeny. The opportunity costs associated with this investment should give us all reason to question the path promoted by some in the UK.[lxxvi]

In similar vein, Marcy Darnovsky, Executive Director of the Center for Genetics and Society, writes: 'Unlike experimental gene therapies where risks are taken by consenting individuals, [MGRT] turns children into biological experiments, and forever alters the human germline in unknowable ways. There is no precedence for this'.[lxxvii] The Council agrees with this assessment, and therefore maintains that in the case of MGRT the wellbeing of future generations must be taken very seriously.

The problem with secular ethics today is that it works with a narrow understanding of obligation based on the transactional or contractual model. According to James Petersen, traditional conception of obligation works on the model of a two-party transaction in which one party provides a service

[lxxv] Ibid., 106.
[lxxvi] Françoise Baylis, 'Ethical Objections to Mitochondrial Replacement', *Impact Ethics*, July 2, 2013.
[lxxvii] Quoted in G Vogel, 'FDA Considers Trials of Three-Parent Embryos', Science, 2014, 343: 827.

and another receives it.[lxxviii] Based on this paradigm, future persons are in principle excluded because he or she is simply unable to fulfil the criterion of promise. The Christian approach, however, requires the idea of obligation to be considerably broadened to include persons who are unable to speak for themselves and to those whom society no longer regards as persons, for example, infants and the severely disabled. According to the Christian view, we have an obligation also to future persons – our children and their children.

Several Christian thinkers have addressed this important issue of the obligations of the present generation to the future generation. For example, Daniel Callahan, in an essay entitled, 'What Obligations Do We Have to Future Generations', insists that to exclude any human being – present or future – from our sphere of responsibility is to invite abuses such as slavery and oppression.[lxxix] Callahan reminds us of the simple fact that the very existence of the future generation depends on us, and that what we do now will affect them for good or for ill. To be responsible for future generations is to pass on to them the benefits that we have received in trust from the generation before us. Donald MacKay has even argued that Jesus' command to love our neighbour as ourselves includes acting responsibly and caringly towards future persons.[lxxx] If loving our neighbour means loving whomever one is able to help, MacKay reasons, then neighbour-love must extend to the future generation, insofar as it is within our powers to enable them to flourish and protect them from harm. Thomas Sieger Derr points out that this concept that we have an obligation to our children and their progeny is not confined to Christianity, but is also found in the other monotheistic religions like Judaism and Islam.[lxxxi]

This sense of responsibility towards the future generation has given us pause when it comes to technology that might possibly bring more harm than good to them. Thus, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research states in its 1982 report, *Splicing Life: The Social and Ethical Issues of Genetic Engineering* that genetic engineering is a 'powerful new tool for manufacturing nature' and carries a reminder of the 'human obligations to act responsibly'.[lxxxii] Although it recognises that genetic engineering has the potential to alleviate human suffering, it cautions against the use of those procedures that would result in inheritable genetic changes in humans. The report issued by AAAS in 2000 entitled, *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues* expresses the same concerns. 'The ability of [Human Genome Germline Modification] to shape the genetic inheritance of future generations', it asserts, 'raises major ethical concerns'.[lxxxiii] In light of these concerns, it recommends that 'Human trials of inheritable genetic changes should not be initiated until techniques are developed that meet agreed upon standards for safety and efficacy'.[lxxxiv] These concerns have led the Convention on Human Rights and Biomedicine published by the Council of Europe in 1997 to prohibit germline modification. Article 13 states 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.[lxxxv]

[lxxviii] James C. Petersen, Genetic Turning Points: The Ethics of Human Genetic Intervention (Grand Rapids, Michigan: Eerdmans, 2001), 311.

[lxxix] Daniel Callahan, 'What Obligations Do We Have to Future Generations?' in *Responsibilities to Future Generations: Environmental Ethics*, ed. Ernest Patridge (Buffalo: Prometheus, 1981), 76.

[lxxx] Donald MacKay, *Human Science and Human Dignity* (Downers Grove, Ill: Inter-Varsity Press, 1979).

[lxxxi] Thomas Sieger Derr, 'The Obligations to the Future', in *Responsibilities to Future Generations: Environmental Ethics*, ed. Ernest Patridge (Buffalo: Prometheus, 1981), 41-2.

[lxxxii] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Splicing Life, The Social and Ethical Issues of Genetic Engineering with Human Beings. 1982. Library of Congress. 2.

[lxxxiii] Frankel and Chapman, 4.

[lxxxiv] Ibid., 10.

[lxxxv] Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm, accessed 18 September 2015.

Harm to Egg Providers

Another ethical concern associated with MGRT is egg donation. It is widely documented that drug-induced egg production and procurement does not only involve time and inconvenience, it also poses considerable risk to the donor. Donors not only have to undergo many hours of screening and counselling, they also have to receive daily hormone injections that can be painful. In addition, hormonal stimulation can cause abdominal pain and cramping, nausea, vomiting and bloating. Other risks include 'rapid weight gain; respiratory difficulty; damage to ovaries, bladder, and bowel; and thromboembolism (as part of the ovarian hyperstimuation syndrome), which in severe cases can be life-threatening'.[lxxxvi] Other possible risks include breast or colon cancer. Furthermore, egg donors also potentially risk psychological harms such as extreme stress and sequelae. One particular concern regarding egg donation is that donors may develop ovarian hyperstimulation syndrome (OHSS). Dr Suzanne Parisan, the former Chief Medical Officer at the FDA lists the risks associated with OHSS:

OHSS carried an increased risk of clotting disorders, kidney damage, and ovarian twisting. Ovarian stimulation in general has been associated with serious life threatening pulmonary conditions in FDA trials including thromboembolic events, pulmonary embolism, pulmonary infarction cerebral vascular accident (stroke) and arterial occlusion with loss of limb or death.[lxxxvii]

Although some have argued that the risks of developing OHSS are low, Annick Delvigne and Serge Rozenberg have pointed out in their discussion of egg donation for fertility treatment that since 'this is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, the syndrome remains a serious problem for specialist dealing with infertility'.[lxxxviii] In addition, Lupron™ (leuprolide acetate), a drug commonly prescribed to egg donors has a range of side effects.[lxxxix]

In a paper titled, Transactional Trade in Human Eggs: Law, Policy and (In)action in Canada', J. Downie and F. Baylis highlight the difference in harm-benefit ratio for people who incur the risks of egg retrieval 'in pursuit of a personal reproductive project' and those who incur the same risks for someone else's project must also be taken into serious consideration.[xc] The authors maintain that in the first case, the harm-benefit ratio is perhaps favourable as the result is having a child. But in the second case, the only benefit is a good feeling that results from an act of altruism. In this latter case, according to the authors, the harm-benefit ratio is not as favourable.

Difficulty in encouraging altruistic donors may result in either coercion or in payment for eggs, both of which are ethically very problematic and should be prohibited, in the view of the Council. Economically disadvantaged women may be targeted as egg providers resulting in their exploitation.[xci] Some of these women may not even understand what donating their eggs involve and the kind of risks they are exposing themselves to. Some may consent to donating their eggs because of the monetary and other forms of incentives offered to them. Obtaining informed consent from donors alone will not protect them from exploitation. As Agnetta Sutton has rightly pointed

[lxxxvi] Alyssa Lane, et al, 'Mitochondrial Replacement Technologies and Germline Nuclear Modification', Society of Obstetricians and Gynaecologists of Canada, 2016, 3.

[lxxxvii] www.ourbodiesourselves.org.

[lxxxviii] Epidemiology and Prevention of Ovarian Hyperstimulation Syndrome (OHSS): A Review', *Human Reproduction Update*, Volume 8, no. 6, 2002, 567.

[lxxxix] They include rash, vasodilation(dilation of blood vessels causing a 'hot flash'), paresthesia (sensation of burning), tingling, pruritis, headache and migraine, dizziness, urticaria (hives), alopecia (hair loss), arthralgia (severe joint pain, not inflammatory in character), dyspnea (difficulty breathing), chest pain, nausea, depression, emotional instability, loss of libido (sex drive), amblyopia (dimness of vision), syncope (fainting), asthenia (weakness), asthenia fravis hypohyseogenea (severe weakness due to loss of pituitary function), amnesia (disturbance in memory), hypertension (high arterial blood pressure), tachycardia (rapid beating of the heart) muscular pain, bone pain, nausea / vomiting. Asthma, abdominal pain, insomnia, swelling of hands, general endema, chronic enlargement of the thyroid, liver function abnormality, vision abnormality, anxiety, myasthenia (muscle weakness), and vertigo. See http://www.fda.gov/medwatch/SAFETY/2004/oct_PI/Lupron_PI.pdf.

[xc] J. Downie and F. Baylis, 'Transnational Trade in Human Eggs: Law, Policy, and (In)action in Canada', *Journal of Law. Medicine and Ethics* 41, 2013, 224-239.

[xci] F. Baylis, 'Babies with some animal DNA in them: a Woman's Choice?' *Int. J. Feminist Approach Bioethics* (2009)2: 75-96.

out: 'To be sure, egg donation raises significant moral and social questions relating to the dignity and health of women, even if the donors come forward voluntarily to offer their services'.[xcii]

The Council has raised some of these objections to egg donation in its response to a BAC Consultation paper in 2008.[xciii] Although the focus of the 2008 BAC consultation was on egg donation for embryonic stem cell research, the ethical issues surrounding oocyte donation for MGRT are similar. The Council points out that the term 'commercial egg donation' is an oxymoron because, as Thomas Murray has shown, those who sell their body tissues should be more accurately described as vendors, not donors.[xciv] The Council notes that terms like 'compensation' and 'payment' commonly used in the literature on egg donation 'are often ambiguous and fluid and must be therefore carefully defined'. But in the main, the Council objects to any kind of payment for bodily parts and tissues because of its view of the sanctity of the human body that such trading violates. 'How we perceive the body is profoundly important because it will influence the policies that we put in place in securing important and valued body tissues', it argues.[xcv]

Biomedical science and technology has in the past quarter of century found many revolutionary lifesaving potentials of the body in medicine as new life is created through reproductive technologies, and lives are sustained through organ and tissue transplant. The image of the body as property has become more prominent now than ever before. But there is a need to ask whether it is appropriate to see the human body through the conceptual lens of 'property', and examine what radical changes are introduced to our sense of self-identity when this paradigm is embraced uncritically.[xcvi]

The Council maintains that although there is nothing intrinsically wrong with buying and selling and that commerce is an important activity that promotes human flourishing, 'life itself must never be viewed as a commodity'. It therefore adds:

Our sense of repugnance is therefore rooted in the belief that some things are simply not for sale. In our society, we recognise that public offices and criminal justice may never be bought or sold. To this list we must include the human body.[xcvii]

Finally, the Council maintains that given the fact that the success rate of MGRT is not fully known at this point and that other alternatives are available for women with mitochondrial disease, the harm-benefit ratio does not favour the encouragement of egg donation. As Alyssa Lane et al have rightly pointed out:

Because the burden of oocyte procurement is high and the immediate benefits of using human oocytes for MRT research is uncertain, it could be unethical to ask women to undergo IVF for this purpose.[xcviii]

CONCLUSION

While the National Council of Churches recognises the plight of women with mitochondrial disease, it cannot endorse or support the legislation and application of Mitochondrial Replacement Technology because of the serious theological, ethical and social issues and concerns associated with this technology.

[xcii] Agnetta Sutton, 'The Moral Cost of Techniques for the Prevention of Mitochondrial DNA Disorder', Catholic Medical Quarterly, 2011, http://www.cmq.org.uk/CMQ/2013/Aug/moral_cost_of_preventing_mitocho.html.

[xciii] Response to the Bioethics Advisory Committee's Consultation Paper entitled Donation of Human Eggs for Research', 2008, http://www.bioethicssingapore. org/images/uploadfile/14457%20PMAnnex%20C%20-%20Written%20Responses.pdf, C29-32.

[xciv] Thomas Murray, 'New Reproductive Technologies and the Family', C.B. Cohen (Ed.), New Ways of Making Babies: The Case of Egg Donation (Bloomington and Indianapolis: Indiana University Press, 1996), 51-69.

[xcv] Response, C-31.

[xcvi] Ibid.

[xcvii] Ibid.

[xcviii] Alyssa Lane, et al, 'Mitochondrial Replacement Technologies and Germline Nuclear Modification', Society of Obstetricians and Gynaecologists of Canada, 2016, 3.

5. National Medical Ethics Committee

MINISTRY OF HEALTH
SINGAPORE

MH 24:63/1-13

19 June 2018

Mr Richard Magnus
Chairman
Bioethics Advisory Committee

Dear Mr Magnus

NMEC'S VIEWS ON THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

We would like to thank the Bioethics Advisory Committee (BAC) for a well-researched and well-presented consultation paper on the ethical, legal and social issues arising from mitochondrial genome replacement therapy (MGRT). We note that the consultation paper makes no explicit recommendations on the clinical application of this therapy and only puts forwards the relevant issues.

2. The NMEC has studied the BAC's consultation paper carefully and our consensus is that the clinical application of MGRT should not be permitted in Singapore at this time. It would be very difficult to make a case for the clinical application of MGRT given the paucity of clinical data. As mentioned in the paper, the first-in-human trials of MGRT have not yet been conducted. This lack of data will preclude the use of most treatments in any field of medicine and not just MGRT in particular. In addition, as shown in Annex A of the BAC's consultation paper, the majority of international policies are in favor of a ban based on the current science. Therefore, the meaningful discussion is whether we should proceed to investigate this intervention in the context of a tightly regulated clinical trial.

Clinical burden

3. The estimated prevalence rate cited in the BAC's paper is 1 in 5,000. It is unclear if this figure includes only mitochondrial DNA disease burden or if it also accounts for nuclear DNA disease burden against which MGRT has no benefit. In addition, mitochondrial diseases may indeed be under diagnosed, but this may be explained by sub-clinical disease burden that has limited therapeutic implications. More data is needed before meaningful decisions can be made.

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Clinical application in the context of any study

4. The question is essentially what measures are justified to fulfill a deep desire for genetically related children in couples who are at risk of producing offspring who may be afflicted by mitochondrial diseases. Can an intervention that is unproven in humans with uncertain long-term risk and impact on resultant children really justify the need to fulfill this particular desire? There is a lack of understanding of the long-term impact of MGRT on the physical health and psychological well-being of the resultant children. In addition, there remain genuine questions about the mismatch between nuclear and mitochondrial DNA caused by MGRT and the possible adverse events that may result as a consequence of this. These risks must be clearly highlighted to anyone undertaking MGRT in any clinical study.

5. Even if under-diagnosis of mitochondrial diseases is accounted for, the clinical burden of mitochondrial diseases is still likely to be small. This raises the ethical issue of distributive justice, as a MGRT clinical study (comprising a long-term follow-up study) would require the investment of a large amount of resources. The proposed use of limited resources to fulfil the desire of a small group of individuals seeking their own genetically related children should be weighed against providing assistance to others who are in more urgent need of medical resources.

6. Furthermore, current but flawed options remain for these couples including pre-implantation genetic diagnosis and prenatal diagnosis. The ethical objections of these options that include the destruction of embryos deemed unsuitable for implantation and elective termination of pregnancy of affected foetuses are noted. However, society in Singapore largely accepts these ethical trade-offs as evidenced by the acceptance of legislation permitting these practices. Therefore, current options must be explored and exhausted before enrolling participants in MGRT.

7. It is not a fair comparison to assess MGRT against in-vitro fertilization because in the latter no modification is made to the germline. Neither is it fair to frame this issue as one of access to MGRT because this is not a medical treatment option but an experimental intervention. Offering desperate couples "hope" in the form of experimental interventions runs the risk of therapeutic misconception in clinical trials and is counterintuitive to our attempts to protect research subjects.

8. Finally, given the lack of longer term understanding of the risks and consequences, any study of MGRT should consider limiting to only male embryos. This will ensure that the previous BAC and NMEC concerns of not modifying the germline are addressed. These concerns include the inadvertent selection against and elimination of genes from the human gene pool that may benefit humans in potentially unknown ways, as well as the tenuous line between germline gene therapy and eugenics.

Recommendation

9. We would urge that the BAC exercises caution in moving forward on the issue of MGRT. Despite under-diagnosis, mitochondrial diseases remain a rare collection of diseases that have devastating clinical impact at the severe end of the spectrum. Some alternatives are already available and should not be discounted despite existing limitations. MGRT clinical data is unavailable and so it cannot be considered a standard medical intervention. Any clinical study must protect vulnerable subjects through tight regulation and be mindful of what we do not really understand.

Yours Sincerely

A/PROF ROY JOSEPH
CHAIRMAN
NATIONAL MEDICAL ETHICS COMMITTEE

Annexe C

6. Singapore Cancer Society

PUBLIC CONSULTATION ON MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

Thank you for inviting Singapore Cancer Society (SCS) to provide views and feedback on the ethical, legal and social issues related to the clinical application of mitochondrial genome replacement technology (MGRT) in humans.

As clearly summarized in the BAC's consultation paper, MGRT is an emerging technology seeking to replace abnormal mitochondria with normal mitochondria through either egg or one-cell embryo manipulation. MGRT aims at preventing the transmission of mitochondrial disease from a mother to her genetically related children, and subsequently avoiding the physical, psychological or social suffering associated with the mitochondrial disorders.

Mitochondrial dysfunctions have been linked with the occurrence of a wide variety of cancers, such as breast cancer, ovarian cancer, colorectal cancer, gastric cancer, and prostate cancer. More scientific studies have to be conducted to understand the exact significance of specific mitochondrial mutations linked with cancer and disease progression. Such evidences would be relevant and helpful to further evaluate the safety of MGRT as well as the management of MGRT clinical applications.

As you are aware, Singapore Cancer Society is a community-based voluntary welfare organisation dedicated to minimising the impact of cancer through research and advocacy, public education, screening, financial assistance, patient services and support, and rehabilitation. Based on our understanding of the MGRT consultation paper, the current impact of MGRT is vague and in the area of biomed ethics. Although there are possible links to certain cancers, it is outside the purview of SCS to comment as it is outside the ambit of our purpose and knowledge.

Tay Kuan Ming
Director, Corporate Services
CEO Office

7. The Law Society of Singapore

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Our Ref: LS/10/RLR/Consultation/2018/BAC/GG/kl/yj
Your Ref: To be advised

29 June 2018

BY EMAIL
bioethics_singapore@moh.gov.sg

Bioethics Advisory Committee Secretariat
1 Maritime Square,
Harbourfront Centre, #11-23,
Singapore 099253

Dear Sir / Mdm,

CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

1. We refer to the Bioethics Advisory Committee Secretariat's (**"BAC"**) email dated 25 April 2018 inviting the Law Society to provide its views on the potential issues related to the clinical application of this emerging technology in humans.

2. The consultation was referred to an Ad-hoc Committee which was set up to respond to two of BAC's previous Consultation Papers. The Committee's views are enclosed in **Annex A**.

3. Thank you for giving the Law Society the opportunity to present our views on this matter.

Yours faithfully,

Genie Sugene Gan (Ms)
Director, Representation and Law Reform Department

Annexe C

The Law Society of Singapore

Annex A

COMMENTS ON THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON MITOCHONDRIAL GENOME REPLACEMENT THERAPY

1. We have been asked by the Law Society of Singapore to provide our comments on the Bioethics Advisory Committee's ("**BAC**") Consultation Paper entitled "Ethical, Legal & Social Mitochondrial Genome Replacement Technology: A Consultation Paper" (**"Consultation Paper"**). As in the Consultation Paper, we will refer to Mitochondrial Genome Replacement Therapy as "**MGRT**".

2. The members of this ad-hoc committee advise and represent individuals and organizations within the healthcare industry as part of their legal work. Some are also members of various ethics committees, including Institutional Review Boards, Clinical Ethics Committees and Transplant Ethics Committees. The members are:
   (i) Ms Kuah Boon Theng SC (Legal Clinic LLC)
   (ii) Ms Rebecca Chew (Rajah & Tann Singapore LLP)
   (iii) Mr Philip Fong (Eversheds Harry Elias LLP)
   (iv) Ms Audrey Chiang (Dentons Rodyk & Davidson LLP)
   (v) Ms Mak Wei Munn (Allen & Gledhill LLP)

3. Our comments on the BAC's Consultation Paper on MGRT are in relation to the following issues:
   a. Is there sufficient evidence supporting MGRT to ensure that "the clinical application of MGRT" will not run foul of Clause B6 of the Singapore Medical Council Ethical Code and Ethical Guidelines (**"ECEG"**) 2016 (i.e. that doctors should not be engaged in "untested practices" and must treat patients only according to generally accepted methods, based on a balance of available evidence and accepted best practices)?
   b. Should MGRT instead be regarded as "innovative therapy" and hence should only be offered in the context of formal and approved clinical trials, which would be subject to the ethics of research?
   c. Are there core ethical concerns regarding MGRT that remain unresolved, for example, whether this can be considered a form of eugenics or alteration of the human germline?

d. Are our current laws sufficiently robust to clarify the rights of the parties involved in MGRT, including whether egg donors could potentially have any rights in relation to the children born from MGRT?
e. Could MGRT give rise to significant risk of potential wrongful life and/or wrongful birth claims in the future?

Untested Practices and the ECEG

4. All medical procedures are associated with some degree of risk. The fact that there may be unknown risks (especially longer term risks) associated with a proposed treatment would not in itself prohibit the offering of such treatments to patients, so long as there is sufficient scientific evidence to support the clinical basis of the treatment, and it is offered only where there are sufficient clinical indications to do so. However, existing laws, regulations and guidelines can prohibit "untested practices". This may occur where there is lack of sufficient data justifying the efficacy and safety of the treatment and therefore insufficient basis to conclude that the risks or uncertainties involved in the treatment would be outweighed by its potential benefits. Treatments could also be prohibited due to the morally or ethically objectionable nature of the treatments themselves.

5. In the Consultation Paper, the BAC explains that international developments in medical science are such that today, some evidence exists to demonstrate that MGRT techniques (MST, PNT and PBT) can not only produce live births, but can successfully reduce the risk of transmission of serious mitochondrial disorders in the process. However, it appears that in spite of these developments, the evidence to date does not allow the scientific community to determine the reasonable criteria for implantation of such embryos that would safeguard the longer term health and mortality of the children born from possibly severe debilitating effects of abnormal mtDNA and symptoms of serious mitochondrial disorders. The complexity of the science involved, taking into account the fact that "[d]ifferent mtDNA mutations have different threshold levels of abnormal mtDNA load which are more likely to produce symptoms" (paragraph 11), the fact that "different individuals may tolerate the same abnormal load differently" (paragraph 11), as well as the phenomenon known as reversion, means that there is as yet no medical consensus on how to determine the criteria by which embryos would ultimately be chosen for implantation, irrespective of whether MST, PNT or PBT is the technique of choice.

6. As for "what rigour and standard of evidence is required to establish safety", one approach referred to in paragraph 75 of the Consultation Paper is to "define a maximum threshold of abnormal mitochondrial DNA (mtDNA) that an embryo can carry, below which any embryo would be deemed safe enough for implantation". At the same time, the Consultation Paper also suggest that due to the "poor correlation between abnormal mtDNA load and manifestation of symptoms", we should accept a "higher-than-threshold" level of risk. The "higher-than-threshold" level is suggested to be anything lower than the "otherwise high level that would be present by natural reproduction" ("**natural risk**").

7. By natural risk, we assume that the BAC is referring to the natural risk *for such parents,* since it is only for these parents where the mothers are carriers that the risk of having a child born with severe mitochondrial disorders can be said to be at an "otherwise high level". However, if "lower than natural risk" is adopted as the criteria for implantation, this would mean that in circumstances where the risk is only slightly lower, the embryo could potentially be selected for implantation, even if it still contains a significant level of abnormal mtDNA. This raises a concern as to whether such a criteria would be considered robust enough to safeguard the children born through these artificial reproduction techniques. Also, such a threshold is far from clear and would encounter challenges when being applied. After all, as the BAC acknowledges, there are other options for such parents [namely (1) adoption; (2) in-vitro fertilisation using healthy donor eggs; (3) pre-implantation genetic diagnosis; and (4) prenatal diagnosis (see paragraph 6)]. If the threshold risk criteria is set too high, it would be difficult for clinicians to offer any reasonable expectation of benefit for the parents who are considering MGRT in favour of other options.

8. Another issue relating to the risks of MGRT is the fact that there are risks posed to future generations. Since mtDNA only passes down through a maternal lineage, it is proposed that these risks be minimised by only allowing the implantation of only male embryos until the "safety and efficacy in the male cohorts [have] been established" (paragraph 48). Limiting implantation to male embryos could be considered a form of sex selection. In general, non-medical sex selection would be regarded as being ethically unacceptable because it is discriminatory. However, it is possible to argue that

there is a clear medical basis to limit implantation to male embryos, to avoid the potentially harmful transgenerational impact of MGRT.

Exception to the Prevailing Prohibition on Altering the Human Germline

9. In February 2015, the UK parliament voted in favour of regulations that would enable mitochondrial replacement techniques to be used in clinical practice in the UK. At the time, there was no universally agreed definition of 'genetic modification' (paragraph 45). It is unclear if the position has since changed. Whilst the issue of whether MGRT results in genetic modification remains open to discussion, it appears non-controversial that MGRT results in human germline alteration, which in the case of female children, will be passed down to future generations.

10. The BAC had 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'" (paragraph 40), pending substantial research on its feasibility and safety. Whilst the Consultation Paper reports some progress on feasibility, again the research on safety appears to be lacking. Serious consideration ought to be given to whether the NMEC's ethical concerns in 2001 (paragraph 41) as to the 'uncertainty over its long-term safety and risks, the inadvertent selection against the 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' have been addressed by good research data.

11. We acknowledge that the BAC has distinguished MGRT from the germline therapies previously discussed on the basis that: (1) in MGRT, only the mitochondrial genome is replaced (leaving the nuclear genome unchanged); (2) the resulting modification is transmissible through the maternal line only. Notwithstanding the distinction, MGRT results in altering the human germline throughout future generations, with the attendant ethical concerns associated with eugenics. The core of the ethical concern has therefore not been addressed. Sex selection as a means of mitigating against this concern would be unacceptable for the reason identified above.

Reproductive Autonomy

12. We note the arguments for reproductive autonomy and the desire to have genetically identical off-spring, which forms the premise underlying the desire for MGRT

(paragraph 54). However, until the scientific and medical communities can be assured that the rights and well-being of the unborn children (through future generations) are not jeopardised in favour of parental reproductive autonomy, we should be cautious about embracing MGRT as the solution. Well-established and accepted alternatives for the exercise of reproductive autonomy (some which provide partial genetic affinity) do exist.

13. Overall, we are of the view that while MGRT is intended to reduce the risk of mitochondrial disease for high-risk patients, ultimately there remains uncertainty regarding MGRT's safety and efficacy and the feasibility of devising a robust clinical treatment protocol, to justify offering this as a clinical treatment option to high risk couples. Specifically, the lack of a clear standard for what would constitute an acceptable threshold risk for implantation, remains a troubling area. In addition, there are also core ethical concerns that have yet to be clearly resolved. For these reasons, we are of the view that in spite of the early evidence supporting the feasibility of MGRT, such treatments should at best be performed only as part of clinical research, where no positive claims regarding the benefits of the treatment should be made, and robust research protocols can be drawn up and consistently applied. The treatment outcomes can then be comprehensively followed up over time. Furthermore, if MGRT is allowed to be performed as part of clinical research, no doubt the respective Institutional Review Boards will have the opportunity to consider if there is a need to ensure that the specific consent of egg donors whose eggs are to be "disassembled" (i.e. have their nuclear DNA/pronuclei removed) has been sought, before the eggs are used for MGRT. It is our view that perhaps with more robust research on MGRT relating to the efficacy and safety of MGRT as a treatment option, one could gather a broader pool of research data covering outcomes under different clinical trials that may provide greater clarity on how to set an acceptable threshold risk for implantation.

Rights and Obligations of Egg Donors

14. It is relevant to consider if the introduction of new assisted reproductive techniques such as MGRT could inadvertently impact the legal rights and obligations of egg donors, as well as the parenthood status of the children born as a result of MGRT. The Consultation Paper (paragraph 72) correctly points out that the Status of Children (Assisted Reproduction Technology) Act (Cap. 317A) (Rev Ed. 2015) provides that the gestational mother would be regarded as the legal mother. Nevertheless, under section

10(2)(d) of the Act, “any other person, with the leave of the court" may apply to the court "for an order to determine the parenthood of a child". The applicants must demonstrate that they have "a sufficient interest in the parenthood of the child notwithstanding that he is not claiming to be treated as the parent of a child or seeking a court order declaring that he be treated as the parent of a child".

15. In our view, an egg donor is unlikely to be said to have “sufficient interest” because there is little genetic affiliation between the child and the donor. Although the egg donor does play a big part in ensuring that the child has a chance of avoiding mitochondrial disease, the donation is arguably more akin to a life-saving blood transfusion or bone marrow or organ donation – while it may save the child’s life, it has no significant impact on the child’s genetic makeup since the donor’s nuclear DNA is not used. Consequently, we believe that the risk of MGRT inadvertently affecting the legal rights and obligations of those involved in the process, such as egg donors, should be regarded as low.

Wrongful Life and Wrongful Birth Claims

16. There is still a lot that is unknown regarding the longer term effects of MGRT. A poor outcome could potentially give rise to wrongful birth or wrongful life claims.

17. Wrongful birth claims are typically brought by parents who claim that the healthcare professional has either failed to inform them of the pregnancy or the fact that the unborn child is likely to be disabled. The claim arises because the mother claims that she would have terminated the pregnancy had she been informed in a timely manner that her child would be disabled. Whether such claims are feasible in the case of MGRT pregnancies would depend on whether there are diagnostic tools that could allow the healthcare professional to screen the fetus-in-utero for mitochondrial disorders and how accurate these tools are.

18. Wrongful life claims are brought for the benefit of children with disabling conditions who claim that they were born as a result of negligence on the part of the healthcare professional. It is not inconceivable that children living with debilitating mitochondrial disease who believe that they are worse off than not having lived at all could have legal actions commenced on their behalf seeking compensation for the injury of being born. Even if their parents had made an informed choice in opting for MGRT, the child may

argue that he never consented to be conceived and to be born to a life of disability. He could even claim that the decision made by his parents to resort to MGRT rather than to conceive a child naturally only served to prolong his own suffering, when a child born without such techniques would have simply passed on naturally from severe mitochondrial disease.

19. There is a dearth of cases in Singapore dealing with wrongful life claims. However, we take reference from *JU and another v See Tho Kai Yin* [2005] 4 SLR(R) 96 (HC), where such a claim was dismissed by the High Court. In doing so, Lai J made reference to the common law position, which is that such wrongful life claims are regarded as being "contrary to public policy as a violation of the sanctity of human life".

20. It would thus appear that where a child born as a result of MGRT has failed to escape the fate of mitochondrial disease, he may have an uphill task in successfully establishing such a claim, and consequently may have no legal remedy in damages. This underscores the need for caution before allowing MGRT to be offered as a clinical treatment option in medical practice, at a time when the safety and long term health of children born through such techniques is still uncertain.

Thank you for giving us an opportunity to provide our inputs on the BAC guidelines.

8. Member of the public

Dear Bioethics Advisory Committee,

Thank you for looking into this ethically sticky issue. I am a high school biology teacher and our curriculum do touch on some fundamental bioethics. However, I am not writing from the perspective of an educator or researcher - anyway there are many differences in views and opinions among the different groups of people.

I am looking at this technology from the perspective of my religion and belief. The '3-parent babies' is strictly speaking equivalent to fornication or adultery and therefore it is out of question for a person of my faith to embrace or condone it.

Currently, I have no statistics or data on genetic diseases that are caused by 'faulty mitochondria'. Even though we may have some studies of them. However, there are many unanswered or largely still unknown questions. E.g. how comprehensive and thorough are these researches and could there be many more undiscovered and unknown genes hidden somewhere or lay dormant within the mitochondrial genome? How much and how in-depth do we know about mitochondrial genes and their long-term effects of the potential babies? Furthermore researchers and doctors are still do not know the risks and possible effects of it. What I am seeing now is that this technology is still at its infancy and we are still largely unprepared to use, not to say to harness it for the benefit of the society.

Thank you for your attention.

Annexe C

9. Mr Darius Lee

12 June 2018

Bioethics Advisory Committee Secretariat
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By email and post
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Dear Sirs,

Submissions on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology"

I refer to the Bioethics Advisory Committee's Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology" dated 19 April 2018.

Enclosed herein are my Respondent's Form and my written submissions on the abovecaptioned matter.

Thank you.

Yours Sincerely,

Darius Lee

Submissions on Mitochondrial Genome Replacement Technology

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A. Introduction

1. Poet and environmental activist Wendell Berry wrote that the question of human limits *"finally rests upon our attitude toward our biological existence, the life of the body in this world"*. What value and respect do we give to our bodies? What uses do we have for them? What relation do we see, if any, between body and mind (or, in more religious terms, body and soul)?[1]

2. The word science is derived from the Latin *scientia*, meaning "knowledge". Science – defined in the Oxford English Dictionary as the intellectual and practical activity encompassing the systematic study of the structure and behaviour of the physical and natural world through observation and experiment[2] – has opened up the possibility of understanding the physical and natural world, including our own bodies, and of using (and thus abusing) it.

3. Scientific progress cannot be unthinkingly equated with moral progress. The modes, methods and purposes for which science is used may have wide ranging moral and social implications. Therefore, the use of science cannot be divorced from the philosophical, ethical and moral underpinnings which not only make science possible, but also make science beneficial.

4. The Bioethics Advisory Committee (the "**BAC**"), in its Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology" dated 19 April 2018 (the "**Consultation Paper**"), has invited comments on whether or not the clinical application of mitochondrial genome replacement technology ("**MGRT**") should be permitted in Singapore for the prevention of heritable mitochondrial disorders.[3]

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[1] Wendell Berry, "The Body and the Earth", online: <https://pages.stolaf.edu/wp-content/uploads/sites/421/2014/08/Berry-BodyEarth-1.pdf> ("***The Body and the Earth***").
[2] Oxford English Dictionary, "science", online: <https://en.oxforddictionaries.com/definition/science>
[3] Bioethics Advisory Committee, Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology" (19 April 2018) (the "**Consultation Paper**") at paras. 2 and 27

5. In these submissions, I will be addressing the ethical, legal and social issues arising from MGRT, and will be arguing that the application of MGRT should not be permitted in Singapore as it fundamentally alters and undermines human identity, family, and what it means to be human. As the efficacy and safety of MGRT are beyond my areas of competence, I will refrain from addressing these, although these issues should be of less relevance in light of the concerns raised herein.

B. Preliminary Objection – Apparent Lack of Neutrality

6. As a preliminary objection, I would like to highlight that, despite the stated purpose of the Consultation Paper, the BAC appears to lean more heavily support of the clinical application of MGRT for the prevention of heritable mitochondrial disorders. There is an apparent lack of neutrality in the manner that the BAC has framed the ethical, legal and social issues.

7. According to the stated purpose of the Consultation Paper, the BAC *"would like to seek public views on whether the clinical application of MGRT should, or should not, be permitted in Singapore."*[4] The BAC has framed the question as such:

> *"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****..."*
> [Emphasis added]

8. Despite such stated purposes, the BAC has clearly stacked the arguments in favour of MGRT, instead of simply presenting the different perspectives for and against MGRT. Although the BAC has acknowledged objections to MGRT, it has been quick to present counter-arguments and rebuttals immediately after stating these objections.

[4] Consultation Paper at 27

9. The table below summarises the BAC's framing of the ethical, legal and social issues:

BAC's Framing of the Ethical, Legal and Social Issues

S/N	Argument	Ref.	Counter-argument presented immediately thereafter?	Ref.
Possible arguments for				
1.	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.	[52]	No	N/A
2.	For some persons with abnormal mtDNA it is their only opportunity to have healthy genetically-related children.	[53]	No	N/A
3.	The significance of having genetically-related children stems from personal autonomy	[54] – [56]	No	N/A
4.	Another reason why MGRT should be allowed is to ensure fair access to technology.	[57]	No	N/A
5.	Welfare of future generations.	[58] – [59]	Yes	[60]
			(But counter-counter-argument is presented)	[61] – [63]
Possible arguments against				
6.	Health or developmental problems.	[65]	Yes	[66]
7.	Undesirable psychological or social effects.	[67] – [68]	Yes	[69] – [72]
8.	Slippery slope.	[77] – [78]	Yes	[76] and [79]

10. In addition, in the context of human trials, the BAC has stated that *"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."[5] [Emphasis added] This is a question-begging statement which puts the cart before the horse, assuming that MGRT is permissible, when the stated purpose of the consultation is purportedly whether MGRT ought to be permissible in the first place.

11. Finally, the BAC has characterised those who disagree with MGRT as *"opponents"* and *"opponents of MGRT"*,[6] rather than reasonable people of goodwill with genuine disagreements. Such confrontational language falls short of the standard of objectivity, neutrality and impartiality in the consultation process expected of a body such as the BAC.

12. To summarise, a careful reading of the Consultation Paper tends to suggest that the BAC has already made up its mind in favour of MGRT, and that this is much less of a consultation as to whether MGRT *"should or should not"* be permitted, than a consultation as to how MGRT should be applied and the ethical guidelines thereto. If this is not so, I would be happy to be proven wrong.

C. Human Nature – Identity, Family and the State

13. At the core of the issue lies a philosophical debate over human nature, particularly a debate over the relationship between the mind (or, in religious terms, the soul) and the body. Who (or what) am I? What is the relationship between "me" and "my body"? Is my body part of who I am? Or am I an unembodied mind inhabiting a physical body, like a "ghost in a shell" (the dualist view)? The answers to these questions have direct implications on our understanding of human identity, family, and thus the ordering of society and the State as a whole.[7]

[5] Consultation Paper at para. 73
[6] Consultation Paper at paras. 75 and 77
[7] See, generally, Robert P. George, "Gnostic Liberalism" *First Things* (December 2016) (***"Gnostic Liberalism"***)

14. It cannot be gainsaid that the ethical, legal and social implications of embracing one perspective or the other are enormous, especially in the context of bioethics and the present discussion regarding MGRT.

15. There are sound reasons to prefer the former view – that the human body is part of the human person – and reject the latter view which views the body as a sub-personal reality inhabited by an unembodied mind.

16. Human beings are "rational animals", a dynamic unity of mind (or soul) and body. The body is no mere extrinsic instrument of the human person (or "self"), but is an integral part of the personal reality of the human being. My body is an essential part of who "I" am and is part of my personal identity across time. For instance, torture and rape are (rightly) considered much more serious and in a different category from offences against property like vandalism or theft; this is because the body is not property, but *personal* in nature and such offences are offences against the *person*. Accordingly, the human person comes into existence at the same time the human organism does (i.e. at conception), and survives – as a person – at least until the organism ceases to be.[8]

17. In normal sexual reproduction, the father's sperm unites with the ovum (or "egg") of the mother to form the zygote. Within the chromosomes of these gametes are the deoxyribonucleic acid ("**DNA**") molecules which constitute the information that guides the development of the new human organism. As the BAC has pointed out, inherited traits are passed down from parent to child through complex biochemical molecules composed of DNA:

> *"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."*[9]

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[8] *Gnostic Liberalism*; see also, Sherif Girgis, Ryan T. Anderson and Robert P. George, *What is Marriage? Man and Woman: A Defense* (New York: Encounter Books, 2012) ("***What is Marriage***") at 24

[9] Consultation Paper at paras. 5 and 6

18. It flows from the above analysis that parenthood is a natural, biological fact. Thus, for example, whether or not a person is the natural father or mother of a child is a question that can be established with a high degree of certainty by virtue of DNA testing.[10]

19. Just as individuals have inherent worth and dignity and are entitled to respect for their human rights, the family unit – comprised of a father, a mother, and their child(ren) – is a natural, pre-political basic building block of society (as opposed to a social construct). To borrow the language of Article 16(3) of the Universal Declaration of Human Rights (the "**UDHR**"), the family is *"the natural and fundamental group unit of society and is entitled to protection by society and the State."*

20. None of this is intended in any way to disparage or undermine the immense value of adoption or adoptive families. Properly understood, the institution of adoption is a child-centric institution intended to *help children find the families they need*, not to help adults "get" the children they want. Article 21 of the Convention on the Rights of the Child ("**CRC**") – to which Singapore is a party – provides that: *"States Parties that recognize and/or permit the system of adoption shall ensure that* ***the best interests of the child shall be the paramount consideration***..." [Emphasis added] It is also worth noting that biology is not irrelevant in adoption; since the consent of the child's biological parents is generally required and is only dispensed with in certain circumstances, and an adoptive child has a legal and moral right to know his or her birth parents.[11]

21. On the other hand, not only is the latter "ghost in a shell" view of the human person unsound philosophically, but essentially demeans human dignity by reducing the human body to a species of property. As the criteria for personhood is usually defined with reference to consciousness or cognitive capacity, it follows that there would be some human beings who are "non-persons".[12]

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[10] See, for example, *ACB v Thomson Medical Pte Ltd and others* [2017] 1 SLR 918 ("***Thomson Medical***") involving an IVF mix-up, where tests including established that the baby had DNA that did not match the appellant's husband's, but an unknown Indian donor; see also, *AD v AE (minors: custody, care, control and access)* [2005] 2 SLR(R) 180 and *WX v WW* [2009] 3 SLR(R) 573

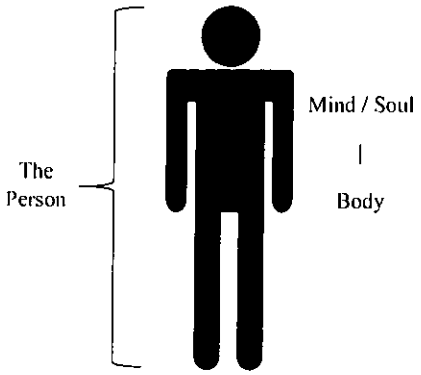
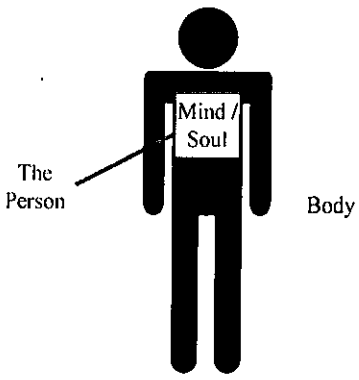
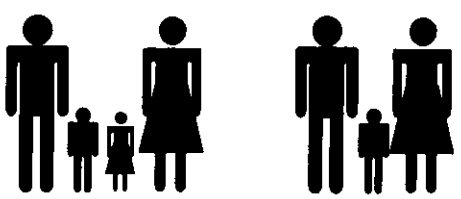
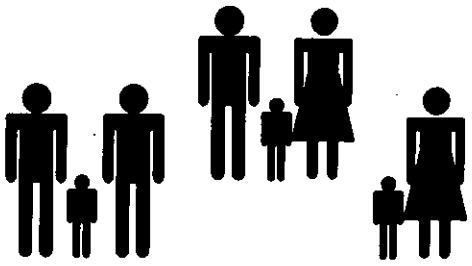
[11] See, for example, section 4 of the Adoption of Children Act; *Melati bte Haji Salleh v Registrar-General of Births and Deaths and another* [1989] 1 SLR(R) 534 ("***Melati***")

[12] This is contrary to Article 16 of the Universal Declaration of Human Rights, which provides, "Everyone has the right to recognition everywhere as a person before the law."; *Gnostic Liberalism*

22. It follows also that, since the body (i.e. biology) is either unimportant or irrelevant, the notion of "family" is redefined, at least in part, as a series of optional associations based on *consent* and *commitment*, which can therefore be dissociated and reconstituted at will. On this view, "family" ceases to be a natural or pre-political institution, instead being a social construct. As a result, the State would be required to recognise, define and demarcate such relations, and the rights and obligations which flow therefrom, including and especially those relating to children. This inevitably results in an expansion of the State, contrary to the principles of limited government.

23. The table below summarises the two opposing views of human nature, as embodied in different perspectives of human identity, family and the State:

Two Opposing Views of Human Nature

Human Identity	
Dynamic Unity	**Dualist View**
	
Family	
Classical	**Revisionist**
Biological connection between father, mother and child(ren) 	Emotional union between committed people 

The State	
Limited Government	**Big Government**
• Family and parent-child relations are natural and pre-political • The State recognises and protects the family unit and parent-child relations	• Family and parent-child relations are social or political constructs • The State defines the family unit and parent-child relations

D. MGRT Fundamentally Alters and Undermines Humanity

24. I submit herein that MGRT fundamentally alters and undermines humanity, and the application of MGRT should not be permitted. In this section, I will begin by (i) highlighting the inherent contradiction and Orwellian doublethink in the BAC's attitude towards parent-child genetic affinity. Thereafter, I will show how MGRT (ii) undermines human identity, (iii) redefines the family, and therefore (iv) expands the role of the State.

(i) Inherent contradiction in BAC's attitude towards parent-child genetic affinity

"Doublethink means the power of holding two contradictory beliefs in one's mind simultaneously, and accepting both of them... The process has to be conscious, or it would not be carried out with sufficient precision, but it also has to be unconscious, or it would bring with it a feeling of falsity and hence of guilt."

- George Orwell,
Nineteen-Eighty-Four

25. There is an inherent contradiction and doublethink in the BAC Consultation Paper's attitude towards genetic affinity between parents and children.

26. On one hand, insofar as the desires of adults are concerned, the BAC has extolled MGRT as the *"**only** opportunity to have healthy genetically-related children"* [Emphasis in original] for some, and added that *"it could be said that the main benefit of MGRT is the fulfilment of such individuals' deep desire to have genetically-related children."* It goes on to argue that *"the significance of having genetically-related*

children stems from personal autonomy", and acknowledges *"the value that society recognises in the desire to have one's genetically-related children"*.[13]

27. On the other hand, the BAC has downplayed the importance of genetic relations when viewing the issue from the child's perspective. While the BAC has referred to the *"emerging concept that understanding one's genetic origins is of great importance in one's personal identity"*, it downplays the importance of genetic identity as *"only one aspect of personal identity; the latter being dependent also on one's upbringing and life experiences."*[14] It proceeds to refer to In-Vitro Fertilisation (**"IVF"**) with donor gametes and adoption, and to argue that *"notions of genetic parents, gestational parents and social parents should no longer be unfamiliar or unacceptable in our community."*[15]

28. The BAC cannot logically, reasonably and fairly hold these two perspectives constant at the same time. It can *either* take the view that genetic affinity between parents and children is valuable, *or* it can take the view that such genetic affinity is unimportant or non-essential; it cannot do both simultaneously without contradicting itself. Likewise, the BAC cannot interpret societal values in such equivocal fashion to be *both for and against* genetic affinity at the same time.

29. It is apparent from this Orwellian doublethink and self-contradiction that BAC is favouring the desires of adults over the needs of children[16] – by appealing to genetic affinity *only insofar as adults' desire to have children is concerned* – which is contrary to fundamental human rights principles, which emphasises that the best interests of children are paramount.[17]

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[13] Consultation Paper at paras. 52 to 56
[14] Consultation Paper at paras. 68 to 69
[15] Consultation Paper at para. 71
[16] The BAC has purportedly framed the issue as one of "balance", that, *"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."* (Consultation Paper at para. 62)
[17] See, generally, CRC

(ii) Undermining human identity

30. Philosophically speaking, the principles in support of MGRT generally regard the human body as a malleable, sub-personal reality which can be shaped at will without undermining the individual. This is a patently false idea, with the result that MGRT effectively undermines human identity by altering the human body, and thus the human *person* for generations.

(a) Altering the human body and identity for generations

31. The BAC has acknowledged that MGRT *"is likely to appear in the genome of all cells in that individual's body"*, and these *"altered genes may be passed down to future generations through that individual's gametes"*.[18] Such irreversible genetic alteration would be unobjectionable if one were to adopt a dualist "ghost in a shell" perspective of the human person,[19] since the alteration does not affect the human *person* on this view.

32. However, for the reasons stated above, such dualism is a false view of human identity. The body is not a sub-personal reality or a "shell" in which we human beings inhabit, but an essential part of the person and his or her personal identity across time. A germline alteration to the human body, which may be passed down to future generations, is not a mere alteration to a sub-personal object (e.g. like a house or car), but a fundamental alteration of the human *person* and subsequent generations of *persons*.

33. The ordinary human experience, even in the context of artificial reproduction, is that every human being derives his or her genetic origin from a father (who contributes the sperm) and a mother (who contributes the egg).[20] As the human body is *part* of the human person, this biological nature is intrinsic to human identity.

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[18] Consultation Paper at para. 22

[19] Indeed, the BAC appears to adopt this view of the human body, on account of its view that genetic identity as "only one aspect of personal identity; the latter being dependent also on one's upbringing and life experiences." (Consultation Paper at para. 69)

[20] For instance, the CRC presupposes that a child has two parents; see generally, Articles 9, 10 and 18 of the CRC

34. MGRT effectively creates a new "type" of human being who derives his or her genetic material from three different people: a father (who contributes the sperm), a mother (who contributes the egg), and a female donor (who contributes the mitochondria).

35. This does not merely redefine human identity for some, but is a fundamental redefinition of human identity for everyone not only in this generation, but for generations to come.

(b) Rights of children, no right "to" a child

36. The arguments in favour of MGRT canvassed in the BAC Consultation Paper rest on the troubling notion that there exists an alleged right to have *"healthy genetically-related children"* of one's own,[21] which is a particular manifestation of the general idea that there exists a so-called right "to" a child.

37. Not only is this alleged right "to" a child – including a *"healthy genetically-related child"* – entirely non-existent anywhere in international law or human rights, the very notion that one human being has a right "to" another human being is repugnant in itself. It objectifies other human beings as property, and – while not equating MGRT with slavery or human trafficking – rests on the same ideology which undergirds slavery and human trafficking.

38. Furthermore, even if there were to exist such an alleged right "to" a child (which in any event is denied), the question remains as to who bears the obligation to fulfil that alleged right. Does the State owe a duty to individuals to help fulfil their desire to have a *"healthy genetically-related child"*? Or do other individuals in society owe such a duty? Both are antithetical to fundamental human rights.

39. Firstly, no individual in society owes a duty to fulfil another individual's desire to have a *"healthy genetically-related child"*. Children are *not* objects, and children's rights are human rights. Every child has a right to know his or her origin, and to know and, as far as possible, be cared for by his or her father and mother. Every child has a right to be

[21] See Consultation Paper at paras. 52 to 57

born free; not bought, sold or manufactured.[22] There is no right "to" a child. Instead, there are the rights *of* children.

40. Secondly, insofar as the obligations of the State are concerned, the State should protect the rights of children and respect the privacy and family life of individuals, by not arbitrarily or unlawfully preventing them from having children of their own.[23] This is a negative obligation (i.e. duty of non-interference), and is far from saying that the State has a (positive) duty to ensure that individuals have *"healthy genetically-related children"* of their own. Indeed, as explained above, the State cannot guarantee the fulfilment of this alleged "right" without objectifying other human beings, especially children.

(c) MGRT is, by definition, the practice of eugenics

41. The advent of the life sciences has opened the door to and accelerated the human quest for genetic perfection. Yet, in this pursuit for "better" and healthier offspring, there is a real risk of undermining the commitment to the intrinsic worth and equality of all human beings – a commitment which underpins all human rights – where the pursuit of genetic perfection may instead usher in an age of genetic discrimination.[24]

42. The term *"eugenics"* is defined by the Oxford English Dictionary as *"The science of improving a population by controlled breeding to increase the occurrence of desirable heritable characteristics"*.[25]

43. Accordingly, the clinical application of MGRT for the prevention of heritable mitochondrial disorders is, *by definition*, the practice of eugenics. There is no doubt that the increase of *"desirable heritable characteristics"* is the end goal in the clinical application of MGRT. The means of *"controlled breeding"* have merely changed.

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[22] Robert Oscar Lopez, "The Call of the Child", in Robert Oscar Lopez and Rivka Edelman, *Jephthah's Daughters: Innocent casualties in the war for family "equality"* (Los Angeles, CA, 2015) 19 at 26; see Articles 7, 8 and 35 of the CRC

[23] See Article 16 of CRC; Article 16 of the Convention on the Elimination of All Forms of Discrimination against Women (**"CEDAW"**)

[24] Eric Cohen and Robert P. George, "The Problems and Possibilities of Modern Genetics: A Paradigm for Social, Ethical, and Political Analysis" (5 July 2011) *The Future of the Constitution* (***"Problems and Possibilities"***) at 11

[25] Oxford English Dictionary, "eugenics", online: <https://en.oxforddictionaries.com/definition/eugenics>

44. Furthermore, Singapore is a party of the Convention on the Rights of Persons with Disabilities ("**CRPD**"), which defines persons with disabilities to *"include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others"*.[26] Persons with disorders arising from mitochondrial dysfunction may in many cases likely be regarded as persons with disabilities within the meaning of the CRPD, since these disorders 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).[27]

45. It is therefore immensely difficult, if not impossible, to reconcile the desire to *"prevent the transmission of inheritable genetic diseases in subsequent generations"*[28] with the promotion of the inherent worth and dignity of persons with disabilities, especially those with disabilities arising from genetic or mitochondrial disorders.

(d) PNT is a violation of individual rights

46. Pronuclear Transfer ("**PNT**") involves the alteration of an already fertilised egg, a zygote.[29] As human life begins at conception (see paragraphs 16 and 17 above), this is a genetic alteration of a distinct, living human being without his or her consent.

47. An in-utero operation on an unborn child (e.g. in cases of spina bifida) may be justified notwithstanding the child's lack of ability to consent on the basis that the surgical intervention is clinically beneficial for the child.[30] However, PNT – as a form of MGRT – differs fundamentally from such surgical intervention as it is a form of genetic modification of the individual person. For this and other reasons elucidated in the rest of these submissions, PNT (and other forms of MGRT) should not be accepted.

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[26] Article 1, Convention on the Rights of Persons with Disabilities ("**CRPD**")
[27] Consultation Paper at para. 9
[28] Consultation Paper at para. 23
[29] Consultation Paper at para. 28
[30] Frank A. Chervenaka and Laurence B. McCullough, "The ethics of maternal-fetal surgery" (2018) 23 Seminars in Fetal & Neonatal Medicine 64

(iii) Redefining the family

48. Next, MGRT redefines the family unit from a natural, pre-political institution to a social or legal construct. It separates people from their genetic origin (which is a loss *per se*), and risks damaging the psychosocial health of individuals conceived through MGRT.

(a) Separating family from biology

49. The classical definition of family – based on the biological connection between father, mother and child(ren) – is grounded on the anthropological truth that men and women are complementary, the biological fact that reproduction depends on a man and a woman, and the sociological reality that children deserve a father and a mother.[31] This is the family structure which best upholds the right of every child to know and, as far as possible, be cared for by his or her father and mother.[32] Genetic relationships are therefore of immense significance to the family unit and the individual person, as a facet of human identity.

50. In the Consultation Paper, the BAC has presented a weak counterargument against the objection that children conceived through MGRT will have *"three parents"*, by merely emphasising that *"the amount of mtDNA that will be inherited from the donor is very small"* and denying any *"critical difference to the social and experiential upbringing afforded to the child"*.[33] It has *not actually denied* the charge that such children would have *"three parents"* and, indeed, it *cannot*. A child conceived through MGRT *would have genetic material from three different people.*

51. Thus, the BAC has instead chosen to make a more radical argument that *"notions of genetic parents, gestational parents and social parents"* should *"no longer be unfamiliar or unacceptable in our community"*,[34] thereby separating family from biology. With due respect, in addition to the points raised about the BAC's doublethink

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[31] Ryan T. Anderson, *Truth Overruled: The Future of Marriage and Religious Freedom* (Washington D.C.: Regnery Publishing, 2015) at 25
[32] Article 7, CRC
[33] Consultation Paper at para. 70
[34] Consultation Paper at para. 71

on genetic affinity and societal values above, the BAC is in no position to redefine or dictate what values society ought to hold in relation to the family.

52. As far as societal values in relation to the family are concerned, Prime Minister Lee Hsien Loong said in Parliament in 2007:

"Singapore is basically a conservative society. The family is the basic building block of our society. It has been so and, by policy, we have reinforced this and we want to keep it so. ***And by "family" in Singapore, we mean one man one woman, marrying, having children and bringing up children within that framework of a stable family unit.***"[35]

[Emphasis added]

53. Even in the context of assisted reproduction through IVF, the Singapore Court of Appeal has observed in *ACB v Thomson Medical Pte Ltd and others* [2017] 1 SLR 918 ("***Thomson Medical***") that, *"persons who consciously choose to undergo IVF do so because of a deep desire to experience, as far as it is possible, the ordinary experience and incidents of parenthood."* This is because:

"129 It is "affinity" – which Norton uses as a convenient shorthand for all those which are partly a result of genetic relatedness and partly a result of the social significance which it carries – which distinguishes familial ties from ties of friendship. ***Put simply, families cannot be thought of as just another social group such as a football club or a running club. This difference lies at the root of why the obligations of parenthood and the relationship between parents and children are so special and socially fundamental: obligations of kinship are inherited and not voluntarily assumed****..."*

[Emphasis added]

54. Reference has been made to the Status of Children (Assisted Reproduction Technology) Act ("**SCARTA**").[36] During the Second Reading of the Bill, the Law Minister

[35] Singapore Parliament Reports, *Penal Code (Amendment) Bill* (23 October 2007) (col. 2398) (Prime Minister Lee Hsien Loong)

[36] Consultation Paper at para. 72

emphasised that the *"real point"* of the legislation was *"to make sure that children who are conceived through the [Assisted Reproduction Technology] process are not left in a legal limbo"*.[37] It is not a sweeping piece of legislation intended to redefine the family unit.

(b) Right to know one's genetic origin

55. It is unfortunate that the Consultation Paper has referred to the concept that *"understanding one's genetic origins is of great importance in one's personal identity"* as an *"emerging concept"*.[38] Contrary to the assertions made in the Consultation Paper, the right to know one's genetic origin is not a mere *"emerging concept"*, albeit the *specific applications* in the context of assisted reproduction may be relatively new.

56. Article 7(1) of the CRC – to which Singapore is a party – provides that:

"The child shall be registered immediately after birth and shall have the right from birth to a name, the right to acquire a nationality and, ***as far as possible, the right to know and be cared for by his or her parents****."*
[Emphasis added]

57. This right to know one's birthparents has, for a long time, been recognised in the context of adoption. As is clear from Article 7(1) of the CRC, it is closely related to the fundamental and natural right of every human being to have his or her own identity.

58. In *Melati bte Haji Salleh v Registrar-General of Births and Deaths and another* [1989] 1 SLR(R) 534 (***"Melati"***), then-Justice Chan Sek Keong (as he then was) ordered the Registrar-General of Births and Deaths to permit the plaintiff to inspect the defunct Adoption of Children Register and make copies of the entries therein relating to her adoption:

[37] Singapore Parliament Reports (12 August 2013) (Minister for Law Mr K Shanmugam)
[38] Consultation Paper at para. 68

*"8 ... In the absence of a demonstrable public interest against disclosure, I would have thought that **it is only morally right that an adopted child in such a position should be granted the right to know who his or her natural parents are**. Indeed there may even be a countervailing public interest in favour of full disclosure in at least one specific circumstance: that of preventing the adopted child from contracting a marriage within any of the prohibited degrees of relationship prescribed by s 10 of the Women's Charter..."*
[Emphasis added]

59. In the case of *Re UKM* [2018] SGFC 20, which concerned a gay man who wished to adopt his child who was conceived through a surrogacy arrangement, District Judge Shobha G. Nair made the following remarks:

*36 ... Even with prosperous advances in technology, a child is born of the union between a man and a woman. That remains today, the starting point of any reasonable discourse on human identity and the rights of individuals... **The adoption court has seen time and again the deep, almost abstruse desire of adopted children to seek the face of their biological parents in an effort to find themselves**..."*
[Emphasis added]

60. This right to know one's genetic origin is a right *per se*,[39] and not contingent on whether or not psychosocial harm exists. On this front, the BAC has regrettably misstated the objection. The issue is not really whether *"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**"* [Emphasis added] or of *"**confusing relationships** with their family members"* [Emphasis added],[40] even though these may be related concerns. The point is not exactly about the child's subjective perceptions or feelings, but that the child suffers *the loss of genetic affinity with his or her mother*, and thereby suffers a *loss of identity*.

[39] In *Melati*, the Court held that, *"if the plaintiff has a right to be informed, it does not matter what her motive is in seeking the information so long as it is not for an illegitimate purpose."* (at para. 8)
[40] Consultation Paper at para. 67

61. Indeed, this is another instance of the BAC's double standards on its definition of "benefit" or "harm" and genetic-relatedness. When promoting MGRT, the BAC considers the *"benefit"* to the *"prospective child"* of *"a substantial genetic relationship with his / her parents"* as a benefit *per se* (i.e. that genetic relationship has intrinsic value), without reference to any psychosocial harm (or benefit).[41] However, when discussing whether the child has three genetic parents, the BAC by a sleight of hand shifts the goal posts and omits to recognise the loss of (part of the) genetic relationship with his or her mother, or the existence of a genetic relationship with the mitochondrial donor, framing the issue instead as one of psychosocial harm (i.e. no intrinsic value to the genetic relationship).[42]

62. In other words, when promoting MGRT, the BAC recognises such genetic relationship as a *right*, but when considering arguments against MGRT, the BAC fails to recognise the loss of such relationship as a harm *per se*, and instead demands proof of psychosocial harm.

63. At its core, the BAC misses the point about the loss of genetic affinity. In the *Thomson Medical* case, the loss suffered by the mother of the child in the IVF mix-up was not about psychosocial harm to herself (or the child) by the error. It was about *the loss of kinship and affinity*. Conversely, a child conceived through MGRT would *lose kinship and affinity* to his or her mother. This is a wound that no declaration by any court or by the law about the legal status of his or her parents can heal.

(c) Evidence of psychosocial harm arising out of loss of genetic affinity

64. Contrary to the BAC's assertions,[43] there is compelling evidence that children are less well-off and suffer psychosocial harm arising out of the loss of genetic affinity.

65. In a United States study of 485 adults between the ages of 18 and 45 years old who said their mother used a sperm donor to conceive them, young adults conceived through

[41] Consultation Paper at para. 59
[42] Consultation Paper at para. 67
[43] See Consultation Paper at para. 71

sperm donation were found to fare worse than children who were raised by their biological parents on a number of counts. These include issues such as:

- Experiencing profound struggles with their origins and identities.
- Family relationships are more often characterised by confusion, tension, and loss.
- Often worry about the implications of interacting with – and possibly forming intimate relationships with – unknown, blood-related family members.
- Twice as likely as those raised by biological parents to report problems with the law before age 25.
- About 1.5 times more likely than those raised by their biological parents to report mental health problems.
- More than twice as likely as those raised by biological parents to report substance abuse problems.[44]

66. Alana S. Newman – who was donor-conceived and founded the Anonymous Us Project[45] to share the experiences of voluntary and involuntary participants in third party reproduction (sperm and egg donation and surrogacy) – wrote in "Children's Rights, or Rights to Children?" (10 November 2014):

"Children whose parents die are given the time, tools, and permission to grieve the loss of their missing parent. People whose parents are absent through sperm and egg donation do not have the luxury to grieve. The overwhelming majority of donor-conceived people do not have photos, video tapes, or letters from their missing parent. Yet we are told we should be grateful. We're told that if our biological parents had been forced to have a relationship with us, then they would never have agreed to give us life.

Since donor-conceived people are not allowed to grieve, we have few safe outlets for talking about our loss, and especially for talking about the inherent shame in how we were conceived. There is an ugly side to our conception: the masturbation, the anonymity, the payment. It's shameful to say, but my father was paid roughly $75 to

[44] Elizabeth Marquardt, Norval D. Glenn, and Karen Clark, "My Daddy's Name is Donor: A New Study of Young Adults Conceived Through Sperm Donation" (2010) The Commission on Parenthood's Future
[45] Read more at Anonymous Us, online: <https://anonymousus.org/>

promise to have nothing to do with me. My mother accepted semen from a total stranger into her body. It is an embarrassing and painful truth."[46]

67. Adoption is a beautiful, life-giving, child-centric institution intended to help children find the families they need. However, even in the context of adoption, there are some indications of higher risks of behavioural health issues among adoptees.

68. The Child Welfare Information Gateway, a service of the U.S. Children's Bureau, has noted in a factsheet on the Impact of Adoption on Adopted Persons (August 2013) that there is a *"divide"* in the research on whether adopted adults' psychological well-being is comparable to their non-adopted peers. However, they added:

"Even with the split in research conclusions about adopted adults' psychological well-being, most of the literature points to adopted adolescents and adults being more likely to receive counseling than their nonadopted peers (Borders et al., 2000; Miller et al., 2000). Studies comparing adopted persons to their nonadopted peers also indicate that adopted adults have similar rates of suicide ideation and attempts (Feigelman, 2005), that adopted adolescents have similar rates of antisocial behaviors (Grotevant et al., 2006), and that adopted persons are at an increased risk of substance use disorders during their lifetime (Yoon, Westermeyer, Warwick, & Kuskowski, 2012)."[47]

69. The factsheet adds that, while adopted persons *"generally lead lives that are very similar to their nonadopted peers"*, *"their adoption experience frequently can contribute to circumstances that the adopted person may need to overcome, such as feelings of loss and grief, questions about self-identity, or a lack of information about their medical background"*.[48]

70. There would be nothing to mitigate if there were no harm. Yet, despite denying evidence of psychosocial harm, the BAC proceeds in the Consultation Paper to suggest

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[46] Alana S. Newman, "Children's Rights, or Rights to Children?" *The Public Discourse* (10 November 2014). online: <http://www.thepublicdiscourse.com/2014/11/13993/>.
[47] Child Welfare Information Gateway, "Impact of Adoption on Adopted Persons" (August 2013). online: <https://www.childwelfare.gov/pubs/f_adimpact.cfm>
[48] Ibid.

ways in which psychosocial concerns may be *"mitigated"*.[49] This is yet another jarring display of the BAC's doublethink and self-contradiction.

(iv) Expanding the role of the State

71. This foray into a brave new world, with its resultant redefinition of human identity and family, necessarily entails the expansion of the role of the State in regulating and defining the rights and obligations of individuals and groups.

72. Biology, including genetic relatedness, is a clear benchmark by which family relations and rights and obligations can be supported and upheld. On the other hand, the concepts of *"genetic parents, gestational parents and social parents"*[50] and the rights and obligations that flow therefrom are not self-evident and not entirely consistent with one another.

73. The State would inevitably be called upon to intervene and demarcate the legal rights and obligations between the different parents *inter se* and between them and the children conceived through MGRT. The BAC has implicitly acknowledged this, by referencing SCARTA as a means of allaying *"confusion about parental status"*.[51]

74. Assuming SCARTA applies in the case of MGRT, the framework of SCARTA is by no means simple or straightforward. Where a declaration is to be made by the Court, the Court must have *"the welfare and best interests of the child"* as *"the first and paramount consideration"* (section 10(3)(a)). Section 10(3)(b) of SCARTA lays down a number of non-exhaustive considerations that the Court must have regard to. These are broad considerations which are fact-specific, case-dependent, and remain to be fleshed out by case law, all of which conduce to litigation.

75. Leaving aside the specifics of how (or whether) SCARTA ought to apply in MGRT, the point here is that MGRT will further expand the role of the State in the family justice

[49] Consultation Paper at para. 72
[50] Consultation Paper at para. 71
[51] Consultation Paper at para. 72. As stated above in paragraphs 55 to 63, this misses the point, since the issue is not exactly that of *"confusion about parental status"*.

system. More state intervention – particularly through the Courts – is required to redress the complicated web of rights and obligations, which are by no means clear. To paraphrase the words of the Chief Justice in a different context: *Where the Court was once a last resort, the family justice system will face more disputes, have more families to assist, and more children to protect.*[52]

E. Conclusion

76. When discussing virtually any ethical, legal and social issue, the question that confronts us time and again remains one and the same, *"What does it mean to be human?"*, along with its related question, *"What does it mean to be humane?"*

77. Ideally and in most ordinary circumstances, even in the context of bioethics, the answer is relatively straightforward. However, on issues such as MGRT which present a fundamental redefinition of – and has wide ranging implications on – human identity, family society and the State, our common humanity is not served by altering the genome of other human beings in pursuit of a more genetically "perfect" version of themselves, however well-intentioned we may be. Therefore, the application MGRT should *not* be permitted in Singapore under any circumstances.

78. Ultimately, what makes us human is not the constant quest or achievement of greater genetic perfection, but in refining humanity through qualities that make us more humane. These include the values of compassion, faith, hope and unconditional love; qualities that can and should be cultivated and passed down to future generations.

Yours Sincerely,

Darius Lee
12 June 2018

[52] Sundaresh Menon CJ, Family Justice Practice Forum: A Vision for Family Justice in Singapore (18 October 2013), online: <https://www.familyjusticecourts.gov.sg/QuickLink/Documents/2013Oct18_FamilyJusticePracticeForum.pdf>

Annexe C

10. Ms Hillary Chua

Response to the BAC's Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology" | Hillary Chua

This response considers whether the clinical application of mitochondrial genome replacement technology (MGRT), also known as mitochondrial donation, should be legalised in Singapore in future, once the benefits of MRGT have been proven to outweigh the risks. Taking a cue from Cynthia Cohen,[i] I surmise that this will be when the risks of harm from MGRT to the resulting child are no greater than the risk of the child being born with mitochondrial disease.

Two potentially-competing interests are discussed in this response: (1) the commercial demand for MGRT; and (2) the role of law, particularly laws on assistive reproductive technologies (ARTs), in defining the values of Singaporean society. While the attractions of the former are substantial, I suggest that as a guiding rule, the latter should be given precedence in deciding whether MGRT should be permitted in Singapore. Applying this rule, I submit that since MGRT is a drastic intervention with human genetic identity and the construction of the nuclear family, legalising MGRT may not be compatible with upholding our national core values.

Market Demand for MGRT

Where there is illness, treatment will be in demand, and where there is a demand, there will be a supply. Understandably, a prospective mother who learns that she is a carrier of abnormal mitochondrial DNA (mtDNA) which could cause her children to suffer from serious mitochondrial disease would be eager to try a technology that is billed as having the potential to *"cancel or reduce the risk of mitochondrial disease."*[ii] The mechanics of the technology and its moral implications are less likely to matter to her than the prospect of treatment. If we were to rely solely on the "yes" of the patient who stands to benefit the most from MGRT, there would be no question about legalising MGRT. Moreover, there are lucrative attractions for Singapore to do so. With Singapore's medical tourism industry losing out to the more cost-effective offerings of our neighbouring countries in recent years,[iii] being the first in the region to provide MGRT services would allow us to stay ahead of the curve in the global marketplace. The international recognition would be tantalising, except that being a hub of affluence is not the only thing that the world knows Singapore for.

'Family as the Basic Unit of Society'

In a 1991 White Paper,[iv] the government established five national core values that would set Singapore apart from the individualised West. One of these values was "family as the basic unit of society", where "family" was defined as comprising one man and one woman, with children. This implies that preserving the traditional family unit is important to our national identity and Singapore's face to the world. Reproductive technologies in particular have the power to redefine "family" by shifting the interplay between social and genetic parenthood. This is true of MGRT. By compositing DNA from both the intended mother and a donor within a zygote or oocyte, MGRT opens the door to a new genetic configuration of family in Singapore. Therefore, the question of whether MGRT should be legalised cannot end with the technology meeting safety standards and there being a market for MGRT. Rather, any proposed laws and regulations concerning MGRT

[i] Cynthia Cohen, 'Designing Tomorrow's Children: The Right to reproduce and Oversight of Germline Interventions' in Audrey R. Chapman and Mark S. Frankel (eds), Designing our Descendants: The Promises and Perils of Genetic Modifications (John Hopkins University Press 2003), 304

[ii] Glenn Cohen, 'Circumvention Medical Tourism and Cutting Edge Medicine: The Case of Mitochondrial Replacement Therapy' (2018) 25 IJGLS 439, 445. This was the wording of the consent form used by Dr John Zhang as a precursor to the world's first live human birth following maternal spindle transfer.

[iii] Linette Lai, 'Singapore tops for medical tourism, but rivals catching up quickly' (Straits Times, 6 June 2017) <https://www.straitstimes.com/singapore/health/spore-tops-f or-medical-tourism-but-rivals-catching-up-quickly> accessed: 8 June 2018

[iv] Singapore Parliament (1991) White Paper on Shared Values (Paper cmd. 1 of 1991)

must first be tested for compatibility with the ethos of our society.

The genetic dimension of Singapore's definition of the "traditional family" is important to this evaluation. The fact that Singapore permits adoption and in-vitro fertilisation (IVF) utilising donor gametes shows that maintaining a genetic link between a child and his/her social parents is non-essential to the Singaporean definition of family. However, in *ACB v Thomson Medical Pte Ltd and others* [2017] SGCA 20, our Court of Appeal established that parents who use donor gametes to conceive are still entitled to experience "genetic affinity" with their child as far as it is possible, by recognising that a loss of genetic affinity could be compensated for at law. Genetic affinity was defined as, among other things, the identification between parent and child through common traits and consanguinity.[v] Under this definition, MGRT could be said to promote genetic affinity for intending mothers who happen to be carriers of mitochondrial disease. This is because, unlike the alternative treatment options, MGRT utilises the intended mother's nuclear DNA (nDNA) (which controls significantly more characteristics compared to mtDNA) in forming an embryo. In this sense, MGRT appears to uphold Singapore's family values by promoting genetic affinity. But what about the presence of the donor's mtDNA in the resulting child? These concerns might be easily dismissed with reference to how the donor's mitochondria are simply naturally-occurring, unmodified organelles that have been transplanted into the child as a matter of treatment.[vi]

However, the above conclusion misses an important point: that an oocyte or embryo containing a combination of the intended mother's nDNA and a donor's mtDNA could never have existed in nature *but* for the intervention of MGRT. The fact that MGRT would result in global changes to the genetic make-up of the resulting child suggests that this reproductive intervention more drastic than, for example, a live patient receiving an organ transplant or a blood transfusion (a distinction that might be obscured by the common language of "donation"). The role of the donor's mtDNA in the ancestry and identity of the resulting child cannot be downplayed. This is especially true in the case of female children who can pass the genetic modification on to the next generation. For these reasons, MGRT would cause a significant change to the interface between social and genetic parenthood within the nuclear family.

When MGRT's potential to promote genetic affinity is weighed against these concerns, MGRT appears to do more harm to the sanctity of the traditional family unit (as it is presently defined in Singapore) than not. As such, a decision against legalising MGRT, in spite of Singapore's technological capacity to do so if it wished, would allow Singapore to make a stand for its founding values in the eyes of the watching world.

Conclusion

In an analysis of reproductive tourism in international surrogacy arrangements, Raywan Deonandan et. al. suggested that "[societies] *should be on the guard for the creeping in of commercial interest into the phrasing of laws meant to define essential societal values."*[vii] This warning applies with equal force to the decision on whether to legalise MGRT. Whilst Singapore prides herelf in being a hub for medical tourism, her lawmakers owe a foremost duty to her people to uphold the values on which this nation was founded, especially in the context of laws on ARTs. On one hand, MGRT appears to promote genetic affinity, but on the other hand, MGRT drastically changes the construction of genetic personhood and parenthood within the nuclear family. Therefore, given the availability of alternatives like adoption or utilising donor gametes, I conclude that there is no compelling reason to legalise MGRT in Singapore in the foreseeable future.

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[v] [2017] SGCA 20 at [128]

[vi] Rosamund Scott & Stephen Wilkinson, 'Germline Genetic Modification and Identity: the Mitochondrial and Nuclear Genomes' (2017) 4 OJLS 886, 900 - 902

[vii] Raywat Deonandan et al, 'Ethical Concerns for Maternal Surrogacy and Reproductive Tourism' (2012) 38 JME 742, 743

Annexe C

Postscript

As I write this, I am mindful of the narrative of "triumph for women" in the recent Irish referendum that overturned the country's constitutional ban on abortion. As the Irish situation illustrates, holding onto a traditional moral objection in the face of widespread national sentiment to the contrary and the accessibility of abortion clinics in neighbouring countries, is not ideal. In these circumstances, the law fails to be an effective deterrent. However, until such time as there is an overwhelming demand for MGRT in Singapore (which seems unlikely, since MGRT caters to a niche in the population), declining to legalise MGRT would be a just measure.

11. Ms Isabel Lim

Dear Sir/ Madam,

My name is Isabel Lim and I am writing to you regarding the public consultation on the ethical, legal and social issues of Mitochondrial Donation.

I wrote my dissertation/ thesis paper on the bioethical considerations of Mitochondrial Donation in my third year of law school in Durham University in 2016. As you would know, this was the period in which the UK was also considering the ethical issues surrounding mitochondrial donation, and was a much debated topic.

As such, I attach here with a copy of my dissertation paper.

In brief, I would set out several points which I think are significant:

1. Ableism

Significantly, Mitochondrial Donation does not save lives per se, but rather advocates for a technique that terminates the life of a defective embryo in place of a healthy one, and is one way society can decide and define what a socially-valuable and socially-functioning individual is.

This is not to say that genetic intervention cannot be pursued, but there is need to adequately balance the medical and social models of disability, such that the rights of disabled persons in Singapore are protected and enhanced, even in the face of advancing medical technology that eradicates defective/ disabled embryos and suggests that such lives are not worthwhile. This is especially important given that there are currently policy efforts to integrate, understand and accept persons with disabilities in Singapore.

2. Access to Mitochondrial Donation

Another potential concern is that only those who can afford this treatment will have access/ better access to this treatment.

Although my dissertation paper was written in the context of the UK and its NHS system, which presumably provides funding for fertility treatment, I believe this UK context nevertheless remains useful.

However, I would submit that this problem of financial accessibility to Mitochondrial Donation is further aggravated in Singapore, precisely because it is not a free healthcare system, where such treatments (let alone novel treatments) would only be accessible to those who can afford it.

3. Risk and Safety Concerns

As with all assisted reproductive technology, there are risk and safety concerns, particularly those that are novel techniques. Therefore, one must be careful of how and what risks of Mitochondrial Donation are strategically portrayed to the public. How do we allay the public's fears? Are we being overly dismissive of the risk and safety concerns? Are we attempting to use personal emotive stories to trump these safety concerns? What is the balance that should be struck?

MST and PNT carry with them a medical/ laboratory history of unsuccessful trials and miscarriages, and these cannot be downplayed.

I have also attached the Respondent's Form.

Annexe C

12. Ms Serene Ho

Submissions on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology (MGRT)"

To the Bioethics Advisory Committee (BAC),

As a woman born with a genetic disorder Osteogenesis Imperfecta, in layman's term "brittle bone disease", I would like to pose the following questions to BAC:

1. Since genes can be edited, can we eliminate ALL genetic disorders? If not, how is it fair that such genetic modification is offered to mothers with mitochondrial disorders but not to mothers of other genetic disorders?

2. Where do we draw the boundary in achieving BAC's seemingly noble goal of "preventing suffering not only for their future children, but also for the prospective parents"?

3. How can BAC or our government prevent the "suffering" of people with acquired disabilities in later life, whether due to accidents, illnesses or old age, if indeed having a disability is equated with suffering?

David Lang, 60 years old, has three children who were born bright and healthy. His children were discovered to suffer from Niemann-Pick disease type C, a rare genetic disorder that causes the cognitive and physical functions of the three children to degenerate. One child died at age 10 while the other two have been left paralysed, unable to talk. Together with his wife Loo Geok, 58, they soldiered on. Mr Lang, who earns less than $5,000 a month, copes financially with the help of family members and church friends and also received money and gifts from strangers. Mr Lang said that his children's ability to smile or respond a little already gave them a lot of joy ("3 kids in family struck by rare genetic disorder"; 20 May).

https://www.straitstimes.com/singapore/3-kids-in-family-struck-by-rare-genetic-disorder
What does BAC have to say to this couple whose joy now is to see their two remaining adult children able to smile and respond a little? Is parental love conditional such that when children are not as "normal" as before, they cease to be their parents' beloved ones?
Family members are meant to "suffer" together. The sacrificial love of a family can weather the storms of life with the help of the society at large. We build a compassionate society not by playing gods but by helping one another through life's upheavals.

MGRT is eugenic in nature. It promotes genetic discrimination in Singapore, at a time when we celebrate the abilities of people with disabilities (PWDs). It is hypocrisy to celebrate PWDs but on the other hand, seek to alter their genes to prevent them from even existing.

I was born with mutated genes that caused me to be born with fractures. I can be said to have "inferior" genes because I was born with a short stature and countless fractures such that my childhood was spent in a Children's hospital. But I was gifted with committed parents who believe in choosing life for me even when I was called a "fragile doll" by medical staff. At birth, I was deemed untouchable and no doctor would have given me a good prognosis.

As medical technology advanced, I had my first surgery at age seven. Now I have rods and metal plates in my femurs. The vicious cycle of more fractures, more surgeries and prolonged periods of rehabilitation dominated my childhood and secondary school years. Despite that, I graduated with a degree in Social Work and Chinese Language and am now a private educator with the ability to

impact lives. I use a wheelchair for greater mobility and to pursue a better quality of life. Using a wheelchair helped me to travel overseas, not only for leisure but also for mission trips.

Education and technology prospered my soul and enabled my body to function at its optimal level. I learnt to swim to build muscle strength. My health record is better than any person without a disability because I choose to take responsibility for my life. Technology can help to improve my life externally. To use technology to tamper with genes is to tamper with nature. The human body is too complex to let us foresee the consequences of tampering with what is unknown. As it is, none of us can even control our every breath.

Doctors know my biology but they know nothing about my life to decide if my life is worth living. I have proven every doctor wrong that a seemingly grossly handicapped baby is now leading a life of victory!

If genes can be readily edited, what have I missed?

Don't healthy people get into accidents and become paralysed? Are their lives no longer worth living?

A New Zealand holiday ended in a horrifying accident and life in a wheelchair. But Jean Ling tells On The Red Dot how she returned to adventuring and found true love ("Left half-paralysed in a holiday crash, she walks at her wedding three years on"; 9 June).

https://www.channelnewsasia.com/news/cnainsider/paralysed-new-zealand-car-crash-jean-ling-wedding-10398902

Don't we love stories of fortitude and know not the boundless magnitude of human strength in times of trials? Are genetically healthy people exempted from the stresses of life and the sicknesses that assail us at different stages of life? Even children are not spared of cancer. In pursuing a more genetically "perfect" version of ourselves, it makes it harder for us to accept any sicknesses or defects caused by accidents or old age.

Finally, children are gifts, not products. MGRT reduces persons to their genetics. For people like me who have a genetic disorder, MGRT signals strongly that those like me who have "defective" genes are not welcome in our nation. Will these therapies be so costly that they exclude the disadvantaged, and may even exacerbate already existing domestic and global socio-economic inequalities? The moral cost of MGRT cannot be justified, no matter how noble the intended goal appears to be. Surely, we can put our limited resources to greater use.

My parents did not pass on defective genes to me. My late mother passed on perseverance and courage to me, to live a life that shines for others.

Let us create a society that looks to the welfare of children first, above the limitless desires and worries of adults.

Yours Sincerely,
Serene Ho (Ms)
14 June 2018

Annexe C

13. Dr John B. Appleby

Response by Dr John B. Appleby (Lancaster Medical School, Lancaster University):

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

The BAC consultation document correctly highlights several of the possible benefits that some might attribute to MGRT, including: avoiding the creation of children with serious mitochondrial disease; avoiding the psychological suffering of parents who are concerned about having children with mitochondrial diseases; and enabling prospective parents to have healthy children that they are genetically related to.

I agree with the BAC that allowing parents to have their 'own' children that they are genetically related to is viewed by many proponents of MGRT as the main benefit and key consideration underlying the development of these techniques (Appleby, 2015; Appleby, 2017; Bredenoord and Appleby, 2017).

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

There are two types of claims that are repeatedly used in the MGRT debate surrounding the significance of genetics and having genetically-related children. These two types of claims focus on the ***qualities*** and ***quantities*** of genes shared between progenitors and their offspring (Appleby, 2017).

First, it is often claimed that the ***quantity*** of genes a person has in common with someone else is significant. For example, some might claim that it is significant that I share approximately half my nuclear genome with my MGRT-conceived child, but it is insignificant that the child shares approximately 37 mitochondrial genes with a donor (Appleby, 2017).

Second, it is often claimed that the ***qualities*** of the genes that a person shares with someone else are significant. For example, some might claim that it is significant that the qualities of the nuclear genes that I share with my MGRT-conceived child may result in us sharing similar physical traits and personal characteristics (Appleby, 2017).

However, ***neither of the above claims about the quantity or qualities of genes shared are convincing arguments*** on their own with respect to why the option to have genetically-related children is important. Both types of claims simply describe a state of affairs rather than describe why that state of affairs is of any importance (Appleby, 2017). If either claim is to be used persuasively to argue for the value of genetic relatedness in the context of MGRT, additional reasons will be required.

The following are some of the additional reasons why some might think the option to have genetically-related children is important:

- Within some religious or ethnic groups there may be stigma towards parents and children who are not genetically related
- Some prospective parents may not only view having genetically-related children via MGRT as matter of respecting their reproductive autonomy (as the BAC has correctly outlined), but these prospective parents may also view this as a matter of respecting their reproductive privacy. Reproduction often occupies a private sphere in people's lives, and giving people the option to exercise their reproductive autonomy (and have genetically-related children if they wish) is a form of respect for their privacy. In short, privacy allows autonomy to flourish.

- Some may view the project of creating offspring that share part of each parent's genome to be of symbolic importance in their lives, in the sense that it could be construed to represent the parents' invested labour and/or responsibility for those offspring (Appleby and Karnein, 2014).

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?

If an MGRT technology is deemed safe and there are adequate resources and expertise to offer MGRT, then it could be argued that it would be unfair to deny women with mitochondrial disorders access to MGRTs. However, in the first human use of any radically new assisted reproductive technology, such as MGRTs, these techniques should be introduced via clinical trial so that data can be gathered in a reliable, transparent and structured manner about the safety of these techniques (Appleby and Wade, 2018). Until adequate safety data is gathered from such trials, the number of prospective participants should be kept small in order to minimise risk to offspring. The UK's Human Fertilisation and Embryology Authority's current licensing conditions for the use of MGRTs could be used as starting point to help determine who should be included and excluded from the initial trial. For example, it would be fair to begin by only offering MGRT to women who are at significant risk of having children that will inherit a serious mitochondrial disease (Appleby, 2015).

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?

The central purpose of MGRT is to have *healthy* children that are genetically-related to their parents. Therefore, it only makes sense that when using these experimental techniques our central focus should be on protecting the welfare of future generations. However, it should also be acknowledged that the welfare of parents and their children is intertwined, and as a result they share many welfare related interests.

It is worth noting that it is highly unlikely that offspring created via MGRT could be harmed because of the monitoring and oversight involved in a clinical trial. In fact, it is likely that the opposite would be true - the children would benefit.

However, we might consider the welfare of future generations beyond the first generation of offspring created via MGRT. For example, suppose the first generation of offspring were created in an MGRT clinical trial and the procedure resulted in some 'carry over' of harmful mitochondria with mutant mtDNA into the resulting embryo. What are the risks of that individual with low levels of harmful mtDNA then reproducing and creating offspring that may have a serious mitochondrial mtDNA disease? One way to avoid such health risks to future generations is to use sex selection to select only male embryos. Because mitochondrial diseases are maternally inherited, selecting only male MGRT-conceived embryos will limit the possible welfare risk of future generations inheriting harmful mitochondrial mtDNA diseases. Sex selection would only need to be used until enough data is been collected from the initial clinical trial(s) to determine the risks to future generations. The number of children conceived this way would be very small and would not impact the gender balance in the population or social attitudes towards gender. In this instance, the benefits of using sex selection to protect the welfare of future generations appear to outweigh any of the costs associated with this approach. This recommendation (Appleby, 2015) has been adopted by the US Institute of Medicine.

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Finally, some have argued that when determining how to spend healthcare resources, the welfare of those individuals with existing mitochondrial diseases should take precedence over any attempt to create new generations of healthy individuals with MGRT. However, I disagree with this view. Society should endeavour to provide the best possible care to those individuals suffering from mitochondrial diseases. But that does not mean MGRT cannot be also be offered (resources and expertise permitting) at the same time to others wishing to have healthy children that they are genetically related to.

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"?

The possible psychological or social impact(s) that MGRT might have on children born via these techniques should not be overlooked; however, this aspect of the MGRT debate has often been overlooked so far.

The next closest thing to MGRT-conceived children and MGRT-conceived families, are families with children conceived with donated gametes and embryos. An extensive body of psycho-social research exists about donor-conceived families and the psychological and social wellbeing of children born using such techniques. What this body of evidence indicates it that children appear to develop normally (both psychologically and socially) in non-traditional family forms and in families where a gamete or embryo donor was used (Appleby et al., 2012; Appleby, 2016).

However, the evidence suggests that in some cases donor-conceived offspring suffer negative psychological and/or social impacts as a result of not being told at an early age about their donor-conception and/or not being able to access identifying information about their donors. The UK HFEA has recommended that any MGRT-conceived children be told at an early age that they were conceived this way. As I argue in detail in my paper (Appleby, 2017), it is possible that MGRT-conceived children will want to know the identity of their donors, in the same way that some donor-conceived people do. In the same paper (Appleby, 2017), I explain in detail how the UK's policy position to treat mitochondrial donors as anonymous is inconsistent (with the law and policy surrounding gamete and embryo donation) and I argue that mitochondrial donors should non-anonymous.

Therefore, ***I recommend that if MGRT is permitted in Singapore, the government should adopt a policy of non-anonymous mitochondrial donation*** (Appleby, 2017). This would be similar to the recent policy recommendation put forward in Australia. This strategy would help to prioritise the psychological and social welfare of MGRT-conceived persons.

The question of whether children conceived through MGRT will have **'three parents'** requires additional clarification. As I have argued extensively in one of my publications (Appleby, 2017), the answer to this question very much depends on what we mean when we say 'parent'. At least five different types of 'parents' exist in MGRT debates about children having 'three parents': biological parents (nuclear DNA contributors); causal parents; legal parents; person's perceived to be parents by offspring (e.g. a donor); and persons with a parental role in the child's life (*for a detailed explanation see* Appleby, 2017). Depending on which version of 'parent' we are referring to, the answer to the 'three parent' question will be different. For example, MGRT-conceived children only have two biological parents. However, it is hard to determine how many individuals will occupy a parental role in the child's life. It is therefore misleading to characterise MGRT-conceived children as having 'three parents' unless we are more precise about what is meant by 'parents' (Appleby, 2017).

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

Serious mitochondrial diseases can cause terrible suffering and death. If MGRT is deemed safe, then it appears that the benefits of avoiding terrible suffering and/or death from serious mitochondrial disease would be enough to justify the first-in-human clinical trials of MGRT. However, anyone willing to use MGRT would likely view the risk of using this radically new technique as something that is outweighed by the benefit of having genetically-related children.

Here it is worth emphasising that MGRT constitute a radical departure from standard assisted reproductive technologies, and they should therefore be introduced through a clinical trial when they are initially made available for human use (Appleby and Wade, 2018). The use of a clinical trial is essential because it offers the structured gathering of scientific data, accountability, transparency and it fosters the trust of the public and other key stakeholders (Appleby and Wade, 2018).

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

It might be possible that allowing MGRT could be viewed as being inconsistent with the prevailing prohibition on altering the human germline. However, guidelines (including prohibitions) should be reviewed regularly to ensure that they are not excluding or inhibiting the use of beneficial biomedical advances, such as MGRTs.

Allowing MGRT can be an ethical exception to the prevailing prohibition on altering the human germline, so long as it is introduced within a well regulated, and transparent framework to monitor clinical use. One reason why allowing the use of MGRTs could be deemed an unethical exception is if it is viewed as lacking adequate regulatory oversight, medical justification and transparency. Each of these areas must be carefully considered in order to preserve society's trust in the process of taking MGRTs from bench to bedside (Bredenoord and Appleby, 2017).

In addition, the BAC is correct to clarify that MGRT involves the replacement of intact mitochondria (along with intact mitochondrial genomes) and does not involve the editing of genomes.

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?

The fact of the matter is that we are not certain that these techniques are equally safe and effective. At this time, perhaps the most notable ethical difference between PNT, MST and PBT is that no children have yet been born following the use of PBT and, in contrast, children have been created with PNT and MST. Importantly, reports so far suggest that the children created with PNT and MST are healthy. Even though PBT is a technique that carries the promise of potentially incurring less 'carry-over' of harmful mutant mtDNA (as compared to MST or PNT), ***PBT remains the most experimental MGRT intervention of the three mentioned above. It may therefore be ethically challenging to justify the use of a highly experimental PBT technique if other somewhat less experimental techniques (e.g. PNT or MST) have be used and have demonstrated to be safe (so far).***

In the future, it would also be beneficial to study the safety of PBT beyond the current 14-day limit on embryo research. I have argued (with Bredenoord - Appleby and Bredenoord, 2018) that the 14-day rule for embryo research should be extended to 28-days in order to extend our understanding of the development and safety of radically new reproductive technologies, such as MGRT.

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As correctly noted by the BAC consultation paper, I have also argued (with Wrigley and Wilkinson - Wrigley *et al.*, 2015) that there are important differences between PNT and MST. For example, PNT is a form of treatment, unlike MST.

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14. Dr Katherine Drabiak

Public Comments to the Singapore Bioethics Committee on the Topic of Mitochondrial Genome Transfer Technology

Submitted by Katherine Drabiak, JD
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June 15, 2018

The Singapore Bioethics Advisory Committee should NOT permit MRGT and should NOT modify its original recommendation against germline genetic modifications set forth in 2005.

INTRODUCTION

I am an Assistant Professor in the College of Public Health at the University of South Florida HEALTH in the United States. My teaching and research focuses in health law, bioethics, and the regulation of emerging technology. I am the author of two comprehensive articles relevant to Mitochondrial Replacement Genome Technology (MRGT, or also referred in this Comment to as Mitochondrial Replacement Therapy or MRT) and human germline modifications.[1]

SUMMARY

1. **Public framing of Mitochondrial Replacement Genome Therapy contains scientific inaccuracies and is misleading.**

Scientists, ethicists, and the media strategically omit crucial risk information, incorrectly describe MRGT as curative, and rely on logical fallacies to obtain public support. Using misleading descriptions undermines the authenticity of the policymaking process.

During discussion in the United Kingdom and the United States, media repeatedly referred to mitochondria as mere batteries of the cell, belying the complex and extensive interaction between mitochondrial and nuclear DNA in evolutionary biology. Ethicists have compared MRGT to a "micro-organ transplantation," alleging there is "no sound basis to oppose MRT" because it constitutes a "cure" so infants can be born without mitochondrial disease.[2]

- MRT is highly risky, experimental, and it is ethically inappropriate to refer to it as curative or a method to prevent mitochondrial disease.
- Touting MRT as a cure for mitochondrial disease is misleading because it will not address most cases. Most instances of mitochondrial disease arise from de novo

mutations and mutations in nDNA.[3] Approximately 80% of mitochondrial disease arises from nDNA mutations, which MRT does not address.[4]

- Appealing to parental suffering relies on a false dilemma fallacy: Proponents for MRGT argue it will prevent incurable genetic disease, save families needless misery, and objections prevent medical progress. Medical research to understand mitochondrial disease or provide more effective therapies does not require sanctioning experimentation on the genomes of future generations.

2. **International law has correctly adopted a principled stance against germline modifications. Singapore's Bioethics Advisory Committee should not modify its stance disallowing germline modifications set forth in 2005.**

MRGT may accurately be classified as nuclear genome transfer and a modification of the human germline, which has prohibited by International Bioethics Committee of the United Nations, The Council of Europe's Convention on Human Rights and Biomedicine, and the European Union's 2001 directive on clinical trials. [5]

Globally, approximately forty countries[6] including Canada,[7] Germany,[8] France,[9] Switzerland,[10] Sweden,[11] and Italy[12] have adopted legislation prohibiting germline intervention on embryos for implantation.[13] Laws enacted in the aforementioned nations not only prohibit germline or heritable modification, but such actions constitute criminal violation subject to fines and or imprisonment.

- Unequivocally prohibiting and criminalizing an action communicates the egregiousness, potential for harm, and social unacceptability of such an action in these nations.
- Nations should reject alarmist rhetoric they are "falling behind": these laws demonstrate many countries acknowledge the lure of technology, but renounce risky experiments that cross the historical bright line of manipulating future generations.[14]
- Prohibitions do not stem from "irrational fear" but instead affirm longstanding precedent based on reasoned deliberation, potential for grave harm, and the principle that no person has the authority to modify the human germline of future generations.

3. **The United Kingdom's process to permit MRGT relied on unsupported scientific assumptions and disregarded credible opposition.**

The Human Fertilisation and Embryology Authority (HFEA) began its consultation process over widespread objections.

- Forty one signatories including notable bioethicists, scholars, and scientists published a letter to the editor of *The Times* in the U.K. expressing alarm over HFEA's proposal for MRT.[15] This letter noted the broad global consensus against germline interventions, stated MRT would "cross the Rubicon" and open the door to other germline modifications, and may pose unforeseen consequences.[16]

4. **The HFEA's Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception assertion that the "evidence does not seem to**

suggest the techniques are unsafe" was not supported by evidence in the policymaking record.[17]

The U.K. Department of Health issued reports and statements describing the process of MRT that strategically characterized the procedure to gain public favor.[18]

- The U.K. Department of Health conceded that MRT constituted a germline modification, but argued that it did not pose a genetic modification because there is not an agreed upon definition of what a genetic modification entails and asserted mtDNA merely functions as batteries of the cell.[19]
- The U.K. Department of Health announced MRT would not contravene the Universal Declaration on the Human Genome and Human Rights' prohibition against germline interventions because it serves a therapeutic corrective purpose so it does not harm human dignity. This characterization failed to account for its highly risky and experimental, not therapeutic, nature.

The HFEA Review acknowledged the potential for complications pertaining to safety and efficacy, but unilaterally dismissed what the scientific community has described as numerous substantial barriers.[20]

- For example, the HFEA Review addressed differential segregation and maternal bottleneck that could result in increasing levels of heteroplasmy during the offspring's course of development in different tissues, and increasing levels of heteroplasmy through subsequent generations.[21]
    - In response to this possibility, the HFEA Review responded -- without explanation -- "there is little evidence of this occurring."[22]
- The HFEA cited animal studies using macaque models where about half of the macaque embryos appeared to develop normally as evidence of "good progress" that MRT appeared to work.[23]
    - In response to the half of embryos following MRT that did not develop correctly, HFEA disregarded these findings, asserting there may be "some differences in embryo development, but nothing has been found to raise concerns of safety."[24]
- The HFEA also noted the concern that there may be incompatibility arising from mixing mtDNA from two sources, but concluded mixing two sources of mtDNA would not pose any complications to interaction with nDNA or cell function.[25]
    - As support for its conclusion, HFEA observed that children from mixed race parents (one source of maternal mtDNA) do not exhibit higher percentages of mitochondrial disease.[26]
    - These circumstances are dissimilar and it is unclear why HFEA considered them comparable.

5. The U.K.'s process dismissed extensive serious scientific concerns raised in public comments.

During the U.K.'s process, the U.K. House of Commons Science and Technology Committee held a hearing on the scientific evidence for MRT and published written correspondence from numerous scientists, physicians, bioethicists, and other stakeholders.[27]

- Although a minority of comments lent support to HFEA's proposed direction and even asserted it would be unethical not to use MRT,[28] the majority of public comments fervently opposed MRT precisely based on unsettling and unresolved issues pertaining to evidence for its safety and efficacy.[29]
- A number of comments highlighted the unpredictability of differential segregation and maternal bottleneck, asserting that attempting to measure carryover of maternal mtDNA in the blastocyst via PGD was an ineffective and improper proxy for predicting long term levels of heteroplasmy and health outcomes.[30]
- Comments also opposed HFEA's characterization of animal models as successful, noting that the 52% of animal embryos that did not develop correctly demonstrated chromosomal abnormalities, and questioned whether these findings may result in unexamined differences in the embryos that scientists proclaimed were developing normally.[31]
- In addition to these responses, multiple comments disputed HFEA's conclusion pertaining to the compatibility of two sources of mtDNA and epigenetic effects resulting from transfer of the nuclear genome from one oocyte or embryo to another.[32]
- A number of interested parties, including the Council for Responsible Genetics, Human Genetics Alert, and several scientific experts submitted similar assessments noting evidence for extensive communication between mtDNA and nDNA expression.[33]
    - Disrupting mtDNA functioning and cross-talk to nDNA directly influences DNA methylation and chromosomal gene expression.[34]
    - Mitochondria are not merely batteries supplying energy to the cell that can be deftly exchanged, but part of a complex interwoven system necessary for the entire organism's subsequent development.[35]
- These observations also highlighted the unprecedented risks related to embryo manipulation, noting the more extreme the level of physical manipulation, the higher the potential for physical damage to the embryo or epigenetic changes resulting from the process of physical manipulation and the risk for functional and developmental health deficits.[36]

6. The U.K.'s policymaking process should not serve as model to other nations because it lacked public consensus and summarily dismissed substantial concerns with safety and efficacy.

- Key shortcomings with the U.K's policymaking process:
    - During the initial proposal, bioethicists, scholars, and scientists voiced dissent because MRT would breach the broad global consensus against germline modifications and urged the government to reconsider.
    - To initially gain favor, the HFEA and the U.K. Department of Health strategically named the techniques MRT rather than accurately describing it as nuclear genome transfer.
    - During the consultation process, numerous scientists provided testimony and correspondence at length relating to safety and efficacy.
    - Scientists objected to HFEA's conclusions based on available evidence, finding not merely a lack of consensus pertaining to safety and efficacy, but that the available scientific evidence demonstrated how unsafe MRT is.

- Despite objections based on international governance, evidence demonstrating insufficient safety and efficacy, and lack of public consensus, British Parliament passed the amendment that would permit HFEA to license fertility clinics to offer MRT.
- This progression reflected a massive disconnect in the legal, scientific, and policymaking process where the policy recommendation and legal change was not supported by the weight of the current scientific evidence.

7. **In the United States, the Cellular, Tissue, and Gene Therapies Advisory Committee of the Federal Food and Drug Administration (FDA) convened a meeting wherein scientists and experts articulated extensive issues with safety, efficacy, and risks.**

The United States has also undertaken steps to begin the process of potentially permitting MRT. In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the Federal Food and Drug Administration (FDA) convened a meeting to discuss scientific risks.

There is currently no legal prohibition against germline modification in the United States (at the time of this Comment, there are federal funding restrictions under the Consolidated Appropriations Act.) Any future clinical investigational use of MRT falls under the purview of the FDA.

8. **Scientific concerns raised in meeting minutes from FDA's 2014 Cellular, Tissue, and Gene Therapies Advisory Committee and current scientific literature do not support investigational clinical applications of MRGT.**

In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA convened meetings to discuss MRT for both the prevention of mitochondrial disease and the treatment of infertility.[37] Participants discussed an extensive list of scientific concerns:

- Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the research subject would be *created* using the proposed methodology.
- There are problems with determining efficacy: testing the blastomere for viability is not indicative of the health of the child and subsequent offspring.[38] One scientist also noted that testing a sample is not indicative of the rest of the inner cell mass, meaning different levels of heteroplasmy may exist, and even subsequently develop at varied rates in different tissues though stages of development and the child's life.[39]
- Animal models have not sufficiently addressed maternal bottleneck, where levels of mutant mtDNA can increase from one generation to the next.[40] This could have an unintended negative impact on future generations.
- Segregation and replication of mtDNA occurs according to its own evolutionary system, which makes predicting subsequent levels of heteroplasmy difficult.[41] Even if segregation initially demonstrates favorable drift toward the donor's mtDNA, these levels may jump unpredictably, or segregate at different levels in tissues throughout the body.[42]

- Levels of mtDNA in the child's blood may reflect a low percent of heteroplasmy, but genetic drift can cause segregation toward the mother's mutated mtDNA in specific tissues or organs, wherein the child may experience diseases arising in those systems.[43]
- Segregation occurs throughout the lifespan of the individual which means low levels of the mother's mtDNA in the child's blood or partial tissue testing would also not reflect the possibility of increasing levels of heteroplasmy later in life resulting in latent presentation of mitochondrial disease.[44]
- Some scientific evidence suggests that segregation appears affected by genetic distance between haplotypes and when haplotypes of maternal mtDNA and donor mtDNA are mixed, reversion toward maternal mtDNA occurs.[45]
    - In animal models, mixed mtDNA has resulted in immune rejection, susceptibility to diseases of metabolism, and deficits in performance and learning capabilities.[46]
- MRGT would disrupt crucial cross-talk between mtDNA and nDNA. Mitochondrial DNA not only functions as a source of energy, but affects a wide range of cellular functioning and how nDNA is expressed.[47]
    - Disrupting the cross-talk between mtDNA and nDNA in animal models results in adverse outcomes and disturbs crucial mitochondrial processes.[48]
    - Current research suggests interference in the communication between mtDNA and nDNA can negatively affect individual development, behavior, susceptibility to disease, and fertility.[49]
    - One scientific article summarized, "perturbation of the mito-nuclear interactions…generally attracts grave consequences."[50]
- Initial positive results (or even a live birth) in Animal and In Vitro Models does not mean human offspring would be "healthy": those studies relied on a small sample and may miss problems that would arise with a larger sample; they did not perform extensive testing for heteroplasmy throughout tissues; the studies did not test germ cells for heteroplasmy or assess the health of subsequent generations; and using sample tests for heteroplasmy as a proxy for health may miss other dysfunction.[51]
- Participants voiced concern that scientific evidence failed to demonstrate safety and efficacy, but that MRT may never be a viable option based on level of risk involved.[52]

- Participants at the 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee reiterated *there are less risky alternatives to having children, and the current evidence falls "far short" of showing MRT would be potentially safe and effective.*[53]

9. **The approach to policymaking in the United States rejected global legal consensus and disregarded serious scientific risks. Nations considering MRGT or germline modifications should examine the adequacy of the policymaking *process*, not only other nation's outcomes or recommendations.**

In 2016 the National Academies of Science, Engineering and Medicine (NAS) authored a consensus report reviewing the ethical, social, and policy considerations relating to MRT for limited circumstances.[54]

- The National Academies of Science, Engineering and Medicine consensus report in the U.S. concluding the potential ethical acceptability for using MRT authored recommendations that were not supported by current scientific evidence.

    - The NAS Report concluded it is ethically permissible for the FDA to conduct clinical investigations subject to a set of conditions including: (1) Initial safety is established and risks to all parties directly involved in the proposed clinical investigations are minimized; (2) Likelihood of efficacy is established by preclinical research; (3) Clinical investigations are limited to women who otherwise are at risk of transmitting a serious mtDNA disease; (4) Intrauterine transfer for gestation is initially limited to male embryos (but may be extended to females if safe and effective); (5) FDA may consider haplotype matching as a means of mitigating risk of incompatibilities between mtDNA and nDNA.[55]
    - This framework dismissed the concerns of multiple experts present at FDA's 2014 meeting who warned of novel risks when experimenting on embryos of future generations:
        - MRT would impact every cell in the body, and there are no methodologies currently to ensure the procedure would not inflict novel abnormalities. [56]
        - Based on available research, scientists cannot currently predict lifetime safety nor latent effects.[57]
        - Such mistakes are both inevitable and irreversible, which means MRT could potentially not only create a congenitally impaired child, but introduce those deficits into the germline of all subsequent offspring.[58]
        - Current research suggests disrupting mtDNA through MRT may have the potential to result in developmental disorders,[59] latent fatalities,[60] expedited aging,[61] increased risk of cancer,[62] as well as unknown abnormalities.[63]
    - The NAS adopted the U.K.'s approach to framing MRT in a favorable manner: it reassured that MRT does not "edit genes" and "there is no direct modification of nuclear DNA" and referred to the procedure as switching mitochondria.
    - The NAS rejected the United Nations Universal Declaration on the Human Genome and Human Rights prohibition against germline modifications. It asserted that referring to the genome as "the heritage of humanity" amounts to "vague and aspirational" language.

10. Strong policymaking requires accuracy, transparency, and honest deliberation of available evidence. Public discussions should include the limitations of experimental technology, alternatives, and risks.

11. MRT would not effectively and sustainably address causes of mitochondrial dysfunction and is not designed to address most cases of mitochondrial disease.

Mitochondrial dysfunction may result from either mtDNA mutations or nDNA mutations. Eighty percent of mitochondrial dysfunction arises from nDNA mutations for which MRT would not address.

Focusing on MRGT presumes technology can and will solve these devastating diseases, but neglects to examine disease root causality and alternatives.

- Recent evidence suggests that a variety of environmental factors induce de novo mutations. Mitochondrial dysfunction is not only a cause of rare fatal disease, but also has been implicated as a factor in the development of common diseases, such as neurodegenerative disease, cancer, diabetes, cardiovascular disease.[64]
- Public health researchers hypothesize that the rising rates of chronic and debilitating disease are a product of environmentally mediated epigenetic damage to our mitochondria.
- In the course of one's life mitochondria are "on the frontline of cellular response to the environment."[65] A variety of environmental agents, including pesticides,[66] heavy metals,[67] antibiotics,[68] pharmaceutical drugs,[69] environmental toxicants such as dioxin[70] and Bisphenol A[71] can all exert changes to mitochondrial integrity and development.
- Over time, exposure to mitochondrial disruptors damages the mitochondria and impacts the resulting health of the individual manifesting as common diseases.[72]
- Effective solutions should address the environmental causes of mitochondrial dysfunction and disease as the means of disease prevention.

12. The push to permit MRGT appears driven by the technological imperative, the desire for scientific ingenuity, and potential commercial profit.[73]

- The campaign to push for MRGT operates within the narrow genomics framework of the technological imperative.
    - When we perceive genes as the problem, biotechnology presents us with the solution.[74]
    - Rhetoric– "cure," "prevent," and "treat"– when repeated continuously "bias us toward acceptance"[75] and represent an Orwellian attempt to re-engineer perception that these "optimistic projections" constitute factual science. [76]
- If nations permit fertility clinics to use MRGT as a "solution" for other diseases such as infertility as performed by physicians in Ukraine and the United States, this holds tremendous commercial potential.
    - The World Health Organization evaluated global rates of infertility, finding up to one quarter of couples of childbearing age suffer from infertility.[77]
    - According to Allied Market Research in the U.S., the global fertility services market was valued at $16,761 million in 2016, and is projected to reach $30,964 million by 2023.[78]
- Commercial markets should not drive the adoption of new experimental technology with this risk profile.
    - The market prioritizes expansion and profit increase as a primary goal, not the best interest of the parties involved.
    - This creates a conflict of interest with parents, children, and egg donors required for MRGT, shifting external costs related to latent risks and long term harm onto parents, egg donors, and children.[79]

13. Recent discussion in Europe calling to reassess the ban on germline modifications should be closely scrutinized because they rely on rhetoric that germline modifications (via MRGT or genome editing) constitute curative therapy, do not sufficiently account for serious scientific risks, and dismiss principled objections.

Managing perception of the science with a particular outcome in mind may impact public acceptance of germline modifications. Though these discussions pertain to genome editing, they are also relevant to MRGT as technology framed as curative that modifies the human germline.

- The INSERM Ethics Committee in France, the German National Academy of Sciences, and the European Academies Scientific Advisory Council adopt the same strategic descriptions such as "correcting" a mutation, "targeted," and "unprecedented accuracy and precision" when referring to genome editing and discuss genome editing's ability to "eventually treat or avoid monogenic disorders."[80]
- In a Letter to the Editor, the European Steering Committee proclaimed no international consensus exists pertaining to germline modifications, labeled a moratorium as "not appropriate," and instead proposed a model for risk matrices to implement "responsible use" of a "promising new technology" [referring specifically to genome editing.][81]
- The Letter to the Editor also explicitly called for nations to reassess the ban against germline modifications previously set forth in the Oviedo Convention.[82]
- Calls for reforming policy and law rely upon the rhetoric and promotional claims of genome editing as a curative therapy, which eclipses the current scientific evidence demonstrating significant risks.
- These meetings occurring within the European Union dismiss historical reasons for the prohibition on germline modifications, which exist as a matter of principle that "no individual or scientist has the moral authority" to experiment with modifying the genome of future humans.[83]

CONCLUSION

Based on global legal consensus against germline modification of human embryos and scientific evidence demonstrating serious risks of MRGT, The Singapore Bioethics Advisory Committee should not permit MRGT nor amend its 2005 stance.

Annexe C

[1] Katherine Drabiak, *Untangling the Promises of Human Genome Editing*, JOURNAL OF LAW, MEDICINE & ETHICS, *forthcoming Fall 2018*; Katherine Drabiak, *Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes*, 20 JOURNAL OF HEALTH CARE LAW, 1-63 (2018).

[2] Julian Savulescu, Mitochondrial Disease Kills 150 Children a Year. A Micro-Transplant Can Cure It, THE GUARDIAN (Feb. 2, 2015), available at: https://www.theguardian.com/science/2015/feb/02/mitochondrial-transfer-micro-transplant-parliamentary-debate.

[3] 59th MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25, 2014), available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390945.pdf (hereinafter "FDA Meeting") at 58-64; *see also* Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations, NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE (2016) (hereinafter "NAS Report") at 27 (discussing mtDNA disease generally relating to later onset milder conditions and nDNA disease constituting earlier onset and more severe expressivity).

[4] *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception: 2014 Update*, HUM. FERTILISATION & EMBRYOLOGY AUTH. at 12 (June 2014) (hereinafter *HFEA Scientific Review*).

[5] Article 9, Directive 2001/20/EC, COUNCIL OF EUROPE (2001), http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

[6] Tetsuya Ishii, Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification, 29 REPRODUCTIVE BIOMEDICINE ONLINE 150, 152-153 (2014); Motoko Araki & Tetsuya Ishii, International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization, 12(108) REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY 9 (2014); Rosario Isasi et al., Editing Policy to Fit the Genome? 351 SCIENCE 337 (2016). See Araki & Ishii at Table S1: Policies on Human Germline Gene Modification for Reproduction Excluding Reproductive Cloning.

[7] Assisted Human Reproduction Act s. 5 (2004); Assisted Human Reproduction Act s. 60 (2004).

[8] Embryo Protection Act, Federal Law Gazette, Part I, No.69 (1990).

[9] Research on Embryos, Bioethics Law, Code of Public Health. Article L2151-5 (2011); Absolute Prohibition on Creating Transgenic Embryos and Chimeras, Bioethics Law, Code of Public Health. Article L2151-2 (2011); *see also* Sylvain Beaumont & Sandra Tripathi, France's Loi du 7 Julliet 2011 Clarifies The Human Embryonic Research System, Life Sciences Bulletin, Fasken Martineau (Aug. 2, 2011), http://www.fasken.com/files/Publication/ad92fa84-d869-497e-80d7-071bfef919e5/Presentation/PublicationAttachment/f3b681c6-78fc-4379-aa6d-19456049955c/Life%20Sciences%20Bulletin%20-%20Beaumont-Tripathi%20-%20August%202%202011.pdf.

[10] Article 35, Federal Act on Medically Assisted Reproduction, Federal Assembly of the Swiss Confederation (1998).

[11] *See* Sections 3-4, The Genetic Integrity Act, Swedish Code of Statutes no.2006:351 (2006).

[12] Article 13, Rules of Medically Assisted Procreation, No. 40 (2004).

[13] Some laws prohibit germline modification to any embryo, some prohibit modification for implantable embryos. *See* Isasi et al., *supra* note 6.

[14] *The Science and Ethics of Genetically Engineered Human DNA*, Hearing Before the Subcommittee on Research and Technology, 114TH CONGRESS (2015).

[15] Letter to the Editor, *Alarm Over Genetic Control of Embryos*, THE TIMES (March 20, 2013), http://www.thetimes.co.U.K./tto/opinion/letters/article3717615.ece.

[16] *Id.*

[17] Mitochondrial Donation: Correspondence Received Relating to the Evidence Hearing on 22 October 2014, SCIENCE AND TECHNOLOGY COMMITTEE, HOUSE OF COMMONS (2014) at 23, 29, 33-49, 73, available at: https://www.parliament.U.K./documents/commons-committees/science-technology/Mitochondrial%20donation/MITCorrespondence.pdf (hereinafter "U.K. Correspondence).

[18] Steve Connor, Scientists Accuse Government of Dishonesty Over GM Babies in Its Regulation of New IVF Technique, THE INDEPENDENT (July 28, 2014), available at: http://www.independent.co.U.K./news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-

babies-in-its-regulation-of-new-ivf-9631807.html; *Mitochondrial Donation: A 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*, U.K. DEP'T OF HEALTH (Feb. 2014) at 13-14, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.

[19] *Id.*

[20] *See generally* U.K. Correspondence, *supra* note 17; FDA Meeting, *supra* note 3.

[21] HFEA Scientific Review, *supra* note 4, at 26.

[22] *Id.*

[23] *Id.* at 20.

[24] *Id.* at 20.

[25] *Id.* at 23, 28-31.

[26] *Id.*

[27] U.K. Correspondence, *supra* note 17.

[28] *Id.* at 7-8. Progress Educational Trust asserted there was prevailing support for HFEA's regulation to permit MRT rationalizing al medical treatment entails experimental results, and it would be unethical not to employ MRT.

[29] *Id.* at 23, 29, 33-49, 48, 73.

[30] *Id.* at 33-35, 50, 64-66.

[31] *Id.* at 23; *see also* Aditi Shah, *"Not Unsafe" Does Not Equal Safe: An Evaluation of the HFEA's Report on MST and PNT*, COUNCIL FOR RESPONSIBLE GENETICS (June 3, 2014), http://www.councilforresponsiblegenetics.org/pageDocuments/Q2M4IDTBFZ.pdf (hereinafter "Council for Responsible Genetics").

[32] U.K. Correspondence, *supra* note 17, at 29, 33-35, 39-49, 53, 64-65, 73.

[33] *Id.* at 33-35, 39-49; Council for Responsible Genetics, *supra* note 31; Human Genetic Engineering on the Doorstep, *Human Genetics Alert* (Nov. 2012) , available at: http://www.hgalert.org/Mitochondria%20briefing.pdf; *Report on the Safety of "Mitochondrial Replacement" Techniques: Epigenetic Issues*, HUMAN GENETICS ALERT (March 2013), http://www.hgalert.org/Report%20on%20the%20safety%20of%20mitochondrial%20transfer.pdf.

[34] *Id.*

[35] *Id.*

[36] *Id.*

[37] FDA Meeting, *supra* note 3; FDA Briefing Document: Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or the Treatment of Infertility, CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25-26, 2014)(hereinafter "FDA Brief").

[38] *Id.*

[39] FDA Meeting, *supra* note 3, at 84-87, 85.

[40] FDA Meeting, *supra* note 3, at 34-35, 141-142; FDA Brief, *supra* note 37, at 7, 21.

[41] *Id.*

[42] *Id.*; Ewen Callaway, *Three-Person Embryos May Not Expel Harmful Genes*, 533 NATURE 445 (2016).

[43] Joerg Patrick Burgstaller et al., mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated By Haplotype Difference and Developmental Stage, 7 CELL REPORTS 2031 at 2031, 2036 (2014)

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[47] FDA Brief, *supra* note 37, at 13

[48] NAS Report, *supra* note 3, at 56.

[49] Human Genetic Alert, *supra* note 33; Reinhardt et al., *supra* note 46, at 1346; *see also* Martin Horan et al., From Evolutionary Bystander to Master Manipulator: The Emerging Roles for the Mitochondrial Genome As A Modulator of Nuclear Gene Expression, 21 EUROPEAN JOURNAL OF HUMAN GENETICS 1335 at 1335-1336 (2013); Rebecca Muir et al., Mitochondrial Content Is Central To Nuclear Genome Expression: Profound Implications for Human Health, 38 BIOESSAYS 150 at 152-153 (2015); Kimberly Dunham-Snary & Scott Ballinger, Mitochondrial-nuclear DNA Mismatch Matters, 349 SCIENCE 1449 (2015).

[50] Horan et al., *supra* note 49, at 1335.

[51] FDA Meeting, *supra* note 3, at 185, 251; Dunham-Snary & Ballinger, *supra* note 49.
[52] FDA Meeting, *supra* note 3, at 248, 261-271.
[53] *Id.*
[54] NAS Report, *supra* note 3, at xiii.
[55] *Id.* at 10-11.
[56] FDA Meeting, *supra* note 11, at 278.
[57] *Id.* at 220.
[58] FDA Brief, *supra* note 37, at 22.
[59] Sarah Knapton, Three Parent Babies Could Be At Greater Risk of Cancer, Warn Scientists, THE TELEGRAPH (Feb. 3, 2015), available at: http://www.telegraph.co.U.K./news/science/science-news/11385370/Three-parent-babies-could-be-at-greater-risk-of-cancer-warn-scientists.html.
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[62] *Id.*
[63] *See also* FDA Meeting, *supra* note 3, at 216 (discussing list of potential risks) and at 278 (discussing the potential for introducing additional abnormalities through MRT).
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[65] Luca Lambertini & Hyang-Min Byun, Mitochondrial Epigenetics and Environmental Exposure, 3(3) CURRENT ENVIRONMENTAL HEALTH REPORTER 214 (2016).
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[67] *Id.*; Kelly Brunst et al., Integrating Mitochondriomics In Children's Environmental Health, 35(9) JOURNAL OF APPLIED TOXICOLOGY 976 at 982-983 (2015).
[68] Sameer Kalghati et al., *Bactericidal Antibiotics Induce Mitochondria Dysfunction and Oxidative Damage in Mammalian Cells*, 5(192) SCIENCE TRANSLATIONAL MED. 192ra85 (2013); Norman Moullan et al., *Tetracyclines Disturb Mitochondrial Function Across Eukaryotic Models: A Call for Action in Biomedical Research*, 10 CELL REPS. 1681 (2015).
[69] Meyer et al., *supra* note 64 at 3-4; Paraskevaidi et al., *supra* note 66.
[70] Meyer et al., *supra* note 64, at 3-4.
[71] Brunst et al., *supra* note 67, at 983.
[72] *Id.* at 3-4; Paraskevaidi et al., *supra* note 66.
[73] *See* Drabiak, *supra* note 1.
[74] N. Comfort, "Can We Cure Disease Without Slipping Into Eugenics?," *The Nation* (July 16, 2015), available at https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/.
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[76] Editorial, "Scientific Buzzwords Obscure Meaning," *Nature* 538, no. 7624 (2016): 140 (stating "buzzwords are Orwellian and obfuscate even as they pretend to enlighten.")
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[79] Sonia Suter, Giving In To Baby Markets: Regulation Without Prohibition, 16 MICHIGAN JOURNAL OF GENDER & LAW 217 at 256-257 (2009).
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[83] Stuart Newman, CRISPR Will Never Be Good Enough to Improve People, *Gene Watch* 30, no.1 (2017): 5-6; George Annas et al., Protecting the Endangered Human: Toward An International Treaty Prohibiting Cloning and Inheritable Alterations, *American Journal of Law and Medicine* 28, no. 2-3 (2002):153-178 at 157-160; Sheila Jasanoff et al., CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation, *Issues in Science and Technology*, Fall 2015, available at: http://issues.org/32-1/crispr-democracy-gene-editing-and-the-need-for-inclusive-deliberation/.

Annexe C

ADDENDUM to:

Public Comments to the Singapore Bioethics Committee on the Topic of Mitochondrial Genome Transfer Technology

Please find attached on the following pages:

Katherine Drabiak, *Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes*, 20 JOURNAL OF HEALTH CARE LAW, 1-63 (2018).

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Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

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Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

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The author would like to thank Spencer Bockover for his research assistance on international law pertaining to human germline modification.

Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

I. Introduction

In the fall of 2016, media headlines reported news of the first baby born as a result of what has been called "three parent IVF" or mitochondrial replacement therapy ("MRT").[1] The initial report indicated Dr. John Zhang, of the New York New Hope Fertility Center worked with a couple from Jordan and traveled to Mexico to perform a procedure called maternal spindle transfer.[2] *New Scientist* first described the "great news" of the first known birth of the child born to the Jordanian couple at risk for mitochondrial disease.[3] Reports asserted the infant "appeared to be healthy," but did not provide substantive evaluation of the infant.[4]

Science Magazine characterized this transnational arrangement as a means for desperate parents who wish to bear a genetically related child free from fatal genetic disease.[5] Media described MRT as a technique that allows parents with rare genetic mutations "to have healthy babies" because it constitutes a "treatment, or even a cure" and praised the courageous Dr. Zhang as a pioneer whose work "should fast-forward progress" against regulatory barriers in the United

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[1] Jessica Hamzelou, *World's First Baby Born With New "3 Parent" Technique*, NEW SCIENTIST (Sept. 27, 2016), https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/; Jennifer Couzin-Frankel, *Unanswered Questions Surround Baby Born to Three Parent*, SCIENCE (Sept. 27, 2016), http://www.sciencemag.org/news/2016/09/unanswered-questions-surround-baby-born-three-parents.

[2] *Id.*

[3] *Id.*

[4] Couzin-Frankel, *supra* note 1; *see also* Sara Reardon, *Reports of "Three-Parent Babies" Multiply*, NATURE NEWS (Oct. 19, 2016), http://www.nature.com/news/reports-of-three-parent-babies-multiply-1.20849.

[5] *Id.*

States.[6] One stem cell biologist asserted regulatory barriers have "[put] novel treatments on the long bench, and therefore it had to be done that way."[7] The British Broadcasting Corporation (BBC) praised Dr. Zhang as acting ethically on his mission to "save lives" and assist families in need of treatment.[8]

Weeks later, more reports surfaced that Dr. Valery Zukin, a physician in Kiev, Ukraine used MRT to "treat" general infertility for two patients in his clinic.[9] Similar to descriptions of Dr. Zhang's actions, *Nature* reported during the pregnancies that Dr. Zukin's technique "seems to have fixed the problem" on the premise that the pregnancy continued to progress.[10] Months later following the birth of the first infant, the media repeated the claim of good news, asserting that after fifteen years of infertility, the patient in Dr. Zukin's clinic finally gave birth to a "healthy baby" that is genetically her own.[11]

MRT described in this article currently refers to two procedures. In the first procedure, maternal spindle transfer ("MST:), the nucleus in the mother's oocyte is removed and transferred

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[6] *Id.;* Alexandra Ossola, *FDA Expected to Approve Technique to Create "The Three-Parent Babies,"* POPULAR SCIENCE (Feb. 3, 2016), http://www.popsci.com/fda-approves-technique-to-create-three-parent-babies.

[7] Reardon, *supra* note 4.

[8] Michelle Roberts, *First "Three Person Baby" Born Using New Method*, BBC NEWS (Sept. 27, 2016), http://www.bbc.com/news/health-37485263.

[9] Andy Coghlan, *"3-Parent" Baby Method Already Used for Infertility*, NEW SCIENTIST (Oct. 10, 2016), https://www.newscientist.com/article/2108549-exclusive-3-parent-baby-method-already-used-for-infertility/.

[10] Reardon, *supra* note 4; *see also* Andy Coghlan, *First Baby Born Using 3-Parent Technique to Treat Infertility*, NEW SCIENTIST (Jan. 18, 2017), https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/.

[11] 59th MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25, 2014), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390945.pdf at 19-21 [hereinafter "FDA Meeting"].

into a donor oocyte whereby the donor oocyte is subsequently fertilized.[12] The second method is referred to as pronuclear transfer ("PNT"), where both the mother's oocyte is fertilized and the donor oocyte is fertilized with sperm in vitro, which creates two zygotes. The nucleus from the fertilized donor zygote is removed and is then replaced with the nucleus from the mother's stage matched zygote.[13] These experimental techniques that promise to "swap in healthy mitochondria" have come under additional scrutiny because MRT entails nuclear genome transfer, which constitutes a modification of the germline that breaches the historical bright line of impermissible interventions on human embryos used for implantation.[14]

Despite a number of international agreements and criminal prohibitions against germline modification in other countries abroad, there is no such legal prohibition in the United States.[15] Last year in the United Kingdom, the Human Fertilisation and Embryology Authority announced it would begin reviewing license applications from fertility clinics that wished to offer MRT to patients as a means to avoid mitochondrial disease. In the United States, the FDA has discussed scientific considerations and the National Academy of Sciences, Engineering, and Medicine

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[12] *Id.*

[13] Rosa Castro, *Mitochondrial Replacement Therapy: the U.K. and US Regulatory Landscapes*, 3 J. OF L. & THE BIOSCIENCES 726, 728 (2016); FDA Briefing Document: *Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or the Treatment of Infertility*, CELLULAR, TISSUE, & GENE THERAPIES ADVISORY COMM., FDA (Feb. 25-26, 2014) [hereinafter "FDA Brief"]; *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, NAT'L ACADS. OF SCI. ENG'G & MED. at 20-21 (2016) [hereinafter "NAS Report"].

[14] *FDA Should Preserve International Consensus Against Human Germline Modifications, Center for Genetics and Society* (Feb. 19, 2014), http://www.geneticsandsociety.org/article.php?id=7528.

[15] Tetsuya Ishii, *Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification*, 29 REPROD. BIOMEDICINE ONLINE 150, 152-53 (2014); Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization*, 12 REPROD. BIOLOGY & ENDOCRINOLOGY 9 (2014); Rosario Isasi et al., *Editing Policy to Fit the Genome?* 351 SCIENCE 337 (2016).

concluded it is ethically permissible to conduct clinical investigations subject to a set of conditions. Notably, FDA discussions have not only considered MRT as a potential investigational method for treating mtDNA disease, but also as an option for treating infertility.

Drawing upon the process in the U.K., this article examines the regulatory framework developed in the U.K., contrasts this system with nations that prohibit or criminalize germline interventions, and describes the regulatory and policymaking discussions that have occurred in the United States. In response to the recent amendments to the law in the U.K. and current reproductive tourism for MRT, this article will describe efforts at public engagement during the policymaking process and the ethical divide pertaining to germline modifications. This article will synthesize the currently known scientific considerations pertaining to safety, efficacy, and risk related to mitochondrial biology, oocyte modification, and oocyte donation. Finally, the article will evaluate the medical rationale provided by proponents that such technology is both necessary and beneficial and consider the impact of commercial interests on the development of MRT.

II. Primer on Mitochondrial Biology

Mitochondria are organelles found in almost every cell in the human body and serve a number of functions including energy production, controlling metabolic processes, and programming cell growth and apoptosis.[16] Far from being mere "batteries" of the cell, scientists now recognize extensive interaction between mitochondrial DNA ("mtDNA") and nuclear DNA

[16] FDA Brief, *supra* note 13, at 5; Anne Claiborne et al., *Finding an Ethical Path Forward for Mitochondrial Replacement*, 351 SCIENCE 668 (2016); Kimberly Dunham-Snary & Scott Ballinger, *Mitochondrial-Nuclear DNA Mismatch Matters*, 349 SCIENCE 1449 (2015); Eli Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832 (2016).

("nDNA") that directly impacts gene expression and cell function.[17] Mitochondria are maternally inherited, and pathogenic mutations in mtDNA can present as a number of serious and potentially fatal diseases.[18] Mitochondrial dysfunction may result in a variety of disorders affecting tissues with a high metabolic demand, such as the brain, heart, muscle, and central nervous system.[19]

Although many individuals in the population may carry mtDNA mutations, these mutations will not result in dysfunction unless the percent of mutant mitochondria reaches a particular threshold.[20] Currently, in the process of both MST and PNT a small percent of cytoplasm is transferred along with the nucleus during the nuclear genome transfer from the mother's oocyte or zygote into the donor's.[21] Although the rate of carryover of mtDNA has been reportedly low, scientists believe the percent of the mother's mutated mtDNA could increase.[22] Scientists refer to the percent mix of mutant mitochondria as degree of heteroplasmy.[23] When cells divide during embryogenesis, gametogenesis, and during the course of normal development, the levels of mutant mitochondria may increase in the dividing cells, which can lead to differential replication and segregation toward a higher degree of heteroplasmy, even in

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[17] FDA Brief, *supra* note 13, at 5; FDA Meeting, *supra* note 11, at 18, 24-31; Klaus Reinhardt et al., *Mitochondrial Replacement, Evolution, and the Clinic*, 341 SCIENCE 1345, 1346. (2013)(discussing the impact of mtDNA on nDNA expression and cross-talk between mtDNA and nDNA).
[18] FDA Brief, *supra* note 13, at 8.
[19] Paula Amato et al., *Three Parent In Vitro Fertilization: Gene Replacement for the Prevention of Inherited Mitochondrial Disease*, 101 FERTILITY & STERILITY 31 (2014).
[20] FDA Meeting, *supra* note 11, at 34-41 (discussing heteroplasmy and disease threshold) and at 66 (hypothesis that we all have naturally occurring heteroplasmy).
[21] FDA Meeting, *supra* note 11, at 21, 123, 168; FDA Brief, *supra* note 13, at 14-15, 20; NAS Report, *supra* note 13, at 47.
[22] FDA Meeting, *supra* note 11, at 34-41
[23] *Id.*

varying levels through different tissues in the body.[24] Scientists describe a phenomenon referred to as maternal bottleneck, defined as when levels of heteroplasmy increase from one generation to the next.[25] For example, a mother with a low level of heteroplasmy who may not display signs of mitochondrial dysfunction and appears healthy could give birth to a child with a high level of heteroplasmy that would reach the threshold and present as mitochondrial disease.[26]

Mitochondrial disease can arise from either mtDNA mutations or nDNA mutations, though inherited mtDNA mutations are rare. According to evidence presented at the Cellular, Tissue, and Gene Therapies Advisory Committee meeting in 2014, maternal transmission of mtDNA disease is rare and only occurs in 1/10,000 individuals.[27] This distinction provides crucial perspective, because failing to distinguish between maternally inherited mtDNA disease and nDNA mitochondrial disease can skew public perceptions of statistical occurrence in a misleading manner. During the public engagement process in the U.K., Human Fertilisation and Embryology Authority characterized the frequency of mitochondrial mutations as affecting 1/200 individuals, and one headline proclaimed nearly 2500 women could benefit from MRT in the U.K.[28] Yet these figures omitted discerning between mtDNA disease and mitochondrial disease resulting from nDNA mutations.[29] Most cases of mitochondrial disease arise from de novo

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[24] *Id.*
[25] *Id.* at 34-35.
[26] *Id.* at 132-35.
[27] *Id.* at 64.
[28] *Human Genetic Engineering on the Doorstep*, HUMAN GENETICS ALERT (Nov. 2012) at 4, http://www.hgalert.org/Mitochondria%20briefing.pdf; *Nearly 2,500 Women Could Benefit from Mitochondrial Donation in the U.K.*, SCIENCE DAILY (Jan. 29, 2015), https://www.sciencedaily.com/releases/2015/01/150129094353.htm.
[29] *See* Francoise Baylis, *The Ethics of Creating Children With Three Genetic Parents*, 26 REPROD. BIOMEDICINE ONLINE 531 (2013).

mutations (new mutations in mtDNA not present in the maternal line) and mutations in nDNA.[30] Approximately 80% of mitochondrial disease arises from nDNA mutations, for which MRT does not address.[31] When subtracting the incidence of nDNA disease, the final potential pool of cases where MRT may apply falls to ten persons a year for the population cited in the discussion pertaining to the U.K.[32]

There is currently no FDA approved treatment for mitochondrial disease.[33] Literature has discussed potential alternative methods designed to avoid mitochondrial disease: adoption, pre-implantation genetic diagnosis ("PGD"), and use of an oocyte donor.[34] Some scholars have rejected adoption and use of an oocyte donor because it overlooks parental desire to bear a genetically related child.[35] PGD may reduce, but not eliminate the chance for a child without mitochondrial disease based on uncertainty of whether the subsequent cellular division would result in genetic drift, defined as increasing rates of mutant DNA and heteroplasmy that reaches the threshold for disease.[36]

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[30] FDA Meeting, *supra* note 11, at 58-64; *see also* NAS Report, *supra* note 13, at 27 (discussing mtDNA disease generally relating to later onset milder conditions and nDNA disease constituting earlier onset and more severe expressivity).
[31] *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception: 2014 Update*, HUM. FERTILISATION & EMBRYOLOGY AUTH. at 12 (June 2014) [hereinafter "HFEA Scientific Review"].
[32] Ishii, *supra* note 15, at 151; *Mitochondrial Donation: Correspondence Received Relating to the Evidence Hearing on 22 October 2014*, SCI. & TECH. COMM., HOUSE OF COMMONS at 15 (2014), https://www.parliament.U.K./documents/commons-committees/science-technology/Mitochondrial%20donation/MITCorrespondence.pdf [hereinafter "U.K. Correspondence"].
[33] FDA Brief, *supra* note 13, at 9.
[34] Baylis, *supra* note 29; FDA Brief, *supra* note, at 10.
[35] Sarah Fogleman et al., *CRISPR/Cas9 and Mitochondrial Replacement Therapy: Promising Techniques and Ethical Considerations*, 5 AM. J. OF STEM CELLS 39 (2016).
[36] Amato et al., *supra* note 19, at 32.

III. International Law and Policy Pertaining to Germline Modification

Contrary to the common parlance discussing the procedure, MRT does not replace mitochondria or "swap in healthy mitochondria," but instead constitutes transferring the nucleus containing 20,000 genes from one oocyte or zygote to another.[37] This procedure is more accurately classified as nuclear genome transfer and a modification of the human germline, which has prohibited by numerous declarations, directives, and laws promulgated by international entities and other nations.[38]

A. United Nations Position on Germline Modification

The United Nations Universal Declaration on the Human Genome and Human Rights has declared that the "human genome underlies the fundamental unity of all member of the human family…it is the heritage of humanity."[39] In Article 5, the Declaration states "research, diagnosis, or treatment affecting an individual's genome shall be undertaken only after rigorous and prior assessment of potential risks and benefits," this intervention requires informed consent that the procedure would be guided by the individual's best interest, and if the individual does not have the capacity to consent then the intervention may only be carried out for the direct benefit or, alternatively, "pose such minimal risk and burden" to the individual that the research is "compatible with the protection of the individual's human rights."[40] These articles do not distinguish between somatic and germline interventions, but suggest a high level of scrutiny

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[37] *3-Person IVF A Resource Page*, CTR. FOR GENETICS AND SOCIETY, http://www.geneticsandsociety.org/article.php?id=6527.
[38] *Id.*; Isasi et al., *supra* note 15; Ishii, *supra* note 15; Araki & Ishii, *supra* note 15.
[39] Universal Declaration on the Human Genome and Human Rights, UNITED NATIONS SCI. EDUC., SCI. & CULTURAL ORG., UNITED NAT'L GEN. ASSEMB. (1997), http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/.
[40] *Id.*

regarding risks must be applied in this area of research and individual consent must be prioritized. These points interpreted together would likely prohibit germline engineering based both on the risk profile and inability for future generations to consent to modification of their genomes.

In subsequent discussions specifically pertaining to the human genome and the appropriate uses of emerging technology, the International Bioethics Committee of the United Nations Educational, Scientific, and Cultural Organization ("UNESCO") promulgated additional guiding principles.[41] Importantly, the International Bioethics Committee noted that the human genome does not constitute raw material that scientists may manipulate at leisure, cautions against genetic reductionism and parsing component parts when attempting to treat the complex nature of human disease while noting the uncertain and highly variable state of the genome and the unpredictable impact of modifications.[42] Recognizing the transnational nature of research, the International Bioethics Committee also directly stated that we should renounce the possibility of scientists acting alone and discourage avenues of regulatory circumvention, in this instance, through reproductive tourism.[43] Finally, the International Bioethics Committee called upon the media to avoid sensationalist journalism, asserted the media's duty to promote scientific literacy, and cautioned that the direction and limitations of science should not be determined by market forces.[44]

Together, these crucial points recognize the complexities of human health and appear to

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[41] Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, UNITED NATIONS SCI. EDUC., SCI. & CULTURAL ORG., UNITED NAT'L GEN. ASSEMB. (2015), http://unesdoc.unesco.org/images/0023/002332/233258E.pdf.
[42] *Id.* at 4.
[43] *Id.* at 3-4.
[44] *Id.* at 4.

caution against precisely the campaign occurring in support of MRT – a risky experimental procedure that separates and patches together building blocks of an embryo heralded by the media a miracle therapy – wherein the media praises physicians engaging in fertility tourism to allegedly dodge unnecessary regulations while generating publicity and expanding a highly profitable commercial market into for patients with infertility.

B. Council of Europe Position on Germline Modification

The Council of Europe has also promulgated several documents pertaining to prohibitions on germline interventions. The Council of Europe's Convention on Human Rights and Biomedicine states "an intervention seeking to modify the human genome may only be taken for preventive, diagnostic, or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants."[45] This Convention clearly demarcates therapeutic somatic interventions as potentially permissible, but unequivocally distinguishes that any germline or inheritable modifications are prohibited. Aligned with this prohibition, in 2001 the European Union promulgated a directive on clinical trials that further specified, "No gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity."[46] Both statements prohibit both clinical trials designed to investigate MRT because it would result in germline modifications.

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[45] Article 13, Convention on Human Rights and Biomedicine, COUNCIL OF EUROPE (1997), https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007cf98.

[46] Article 9, Directive 2001/20/EC, COUNCIL OF EUROPE (2001), http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

C. Comparing U.S. Governance Pertaining to Germline Modification to Other Nations

Globally, approximately forty countries[47] including Canada,[48] Germany,[49] France,[50] Switzerland,[51] Sweden,[52] and Italy[53] have adopted legislation prohibiting germline intervention on embryos.[54] Laws enacted in the aforementioned nations not only prohibit germline or heritable modification, but such actions constitute criminal violation subject to fines and or imprisonment. Unequivocally prohibiting and criminalizing an action communicates the egregiousness, potential for harm, and social unacceptability of such an action in these nations. Unlike the widespread alarmist rhetoric that the United States is "falling behind" and failing to invest in promising genomic technologies, these laws demonstrate the opposite: many countries acknowledge the lure of technology, but renounce risky experiments that cross the historical

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[47] *See* Araki & Ishii, *supra* note 15, at Table S1: Policies on Human Germline Gene Modification for Reproduction Excluding Reproductive Cloning.
[48] Assisted Human Reproduction Act § 5 (2004); Assisted Human Reproduction Act § 60 (2004).
[49] Embryo Protection Act, Federal Law Gazette, Part I, No.69 (1990).
[50] Research on Embryos, Bioethics Law, Code of Public Health Article L2151-5 (2011); Absolute Prohibition on Creating Transgenic Embryos and Chimeras, Bioethics Law, Code of Public Health. Article L2151-2 (2011); *see also* Sylvain Beaumont & Sandra Tripathi, *France's Loi du 7 Julliet 2011 Clarifies The Human Embryonic Research System*, LIFE SCIENCES BULLETIN, Fasken Martineau (Aug. 2, 2011), http://www.fasken.com/files/Publication/ad92fa84-d869-497e-80d7-071bfef919e5/Presentation/PublicationAttachment/f3b681c6-78fc-4379-aa6d-19456049955c/Life%20Sciences%20Bulletin%20-%20Beaumont-Tripathi%20-%20August%202%202011.pdf.
[51] Article 35, Federal Act on Medically Assisted Reproduction, Federal Assembly of the Swiss Confederation (1998).
[52] *See* Sections 3-4, The Genetic Integrity Act, Swedish Code of Statutes no.2006:351 (2006).
[53] Article 13, Rules of Medically Assisted Procreation, No. 40 (2004).
[54] Some laws prohibit germline modification to any embryo, some prohibit modification for implantable embryos. *See also* Isasi et al., *supra* note 15; Anna Zaret, *Editing Embryos: Considering Restrictions on Genetically Engineering Humans*, 67 HASTINGS L. J. 1805, 1810-11 (2016).

bright line of manipulating future generations.[55]

Canada's Assisted Human Reproduction Act in particular contains notable provisions that prioritize central concepts to guide appropriate application of technology relating to reproductive and genomic interventions.[56] Section 2 of Canada's Assisted Human Reproduction Act states that the "health and well-being of future children must be given priority," and that the Parliament seeks to uphold the "protection of human health, safety, dignity and rights" relating to the use of assisted reproductive technologies, and prohibits compensation for oocyte donors due to the potential for health risks and exploitation.[57] Further, Subsection (g) of Section 2 explicitly states "the integrity of the human genome must be preserved and protected."[58] These provisions together recognize the commercial nature of technology and declare neither commercial nor other interests, such as the technological imperative, ought to drive the adoption of technology and modification of the germline is prohibited.[59]

In 2015, the National Academy of Sciences, Engineering and Medicine, the Royal Society, and the Chinese Academy of Sciences sponsored the International Summit on Human Gene Editing to discuss broader issues relating to gene editing and modification of the

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[55] *The Science and Ethics of Genetically Engineered Human DNA*, Hearing Before the Subcommittee on Research and Technology, 114TH CONGRESS (2015). Rather than discussing human dignity or risks of technology, attendees at this hearing pled for federal funding, noted the global market competitiveness, and asserted regulation must not "squelch the science" or the United States would "fall behind." Attendees also mischaracterized the experimental nature of germline modification, asserting that parents merely have a "desire to protect their children" [by modifying their genomes] and there may be a time when we consider it unethical not to modify our children's genomes.

[56] Assisted Human Reproduction Act § 2 (2004).

[57] *Id.*

[58] *Id.*

[59] *Id.*

germline.[60] Though the meeting discussed recent research relating to other genetic modification technologies such as CRISPR, many of the considerations are also applicable to MRT. The National Academies Press published a meeting summary that called for a moratorium on clinical germline modification, noting safety and efficacy issues are unresolved, and such action could impose irreversible risks and long term harms.[61] Commentators at the International Summit also recognized the potential for economic interests to capitalize on the global nature of science and technology, where technology adopted in one location prompts international forum shopping. [62]

Situating the actions of Dr. Zhang and Dr. Zukin against the backdrop of the global climate where many nations not only prohibit, but impose criminal penalties for these risky experiments it becomes exceedingly clear how radical these events were. Numerous scientists, bioethicists, and policymakers swiftly voiced vehement opposition, asserting that "going rogue" was "irresponsible and unethical" because it combined reproductive tourism promoting commercial interests with "highly experimental science."[63] These characterizations stand in stark contrast to media articles praising Dr. Zhang, decrying slow "progress" in the United States, and

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[60] International Summit on Human Gene Editing: A Global Discussion, NAT'L ACAD. OF SCI., ENG'G & MED. (2015), https://www.nap.edu/catalog/21913/international-summit-on-human-gene-editing-a-global-discussion.

[61] *Id.*

[62] *Id.*

[63] *Comment on the Use of Mitochondrial Manipulation Techniques by US Scientists in Mexico*, CTR. FOR GENETICS & SOC'Y (Sept. 27, 2016), http://www.geneticsandsociety.org/article.php?id=9697; *Comment on "3-Person IVF" Procedures Reportedly Conducted in Ukraine*, CTR. FOR GENETICS & SOCIETY (Oct. 10, 2016), http://www.geneticsandsociety.org/article.php?id=9730; *3-Person IVF A Resource Page*, *supra* note 37; *see also* Paul Knoepfler, *First 3-Person IVF Baby Born Via "Rogue" Experiment in Mexico Clinic? The Niche* (Sept. 27, 2016), https://ipscell.com/2016/09/first-3-person-ivf-baby-born-via-rogue-experiment-at-mexico-clinic/; Pete Shanks, *Wrong Steps: The First One From Three*, DECCAN CHRON. (Oct. 2, 2016), http://www.deccanchronicle.com/lifestyle/viral-and-trending/021016/wrong-steps-the-first-one-from-three.html.

intimating these procedures constitute an effective "treatment, or even cure."[64] Perpetuating such bias and gross mischaracterization in scientific media deliberately skews the framing of the discussion as an intentional means to gain favor and direct the outcome. This campaign not only lacks transparency, but promotes a policymaking process premised upon inaccurate scientific information and false characterizations of global legal consensus that renders it egregiously unethical. Furthermore, Dr. Zhang's actions to evade regulatory structures in the United States by performing MRT in Mexico were precisely the type predicted by the International Summit, and will likely continue to occur based on a public statement from the New Hope Fertility Center branch in Mexico promising plans for more "three-parent babies."[65]

IV. United Kingdom's Process to Permit MRT

In 2013, the Human Fertilisation and Embryology Authority (HFEA) began its consultation process to consider the process of permitting MRT. The HFEA is the entity in the U.K. that oversees reproductive technologies such as IVF and commercial surrogacy and promulgates criteria for licensing fertility clinics.[66] During the policymaking process in the United Kingdom, scientists, bioethicists, and other stakeholders raised concerns about how both the British media, the U.K. Department of Health, and the HFEA presented MRT to the public.[67]

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[64] Ossola, *supra* note 6; Michael Le Page, *Mexico Clinic Plans 20 "Three-Parent" Babies in 2017*, NEW SCIENTIST (Dec. 9, 2016), https://www.newscientist.com/article/2115731-exclusive-mexico-clinic-plans-20-three-parent-babies-in-2017/.

[65] *Id.*

[66] Castro, *supra* note 13; 3-Person IVF: A Resource Page, *supra* note 37; About the HFEA, Human Fertilisation and Embryology Authority, http://www.hfea.gov.U.K./25.html.

[67] *See generally* Steve Connor, *Scientists Accuse Government of Dishonesty Over GM Babies in Its Regulation of New IVF Technique*, THE INDEPENDENT (July 28, 2014), http://www.independent.co.U.K./news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-babies-in-its-regulation-of-new-ivf-9631807.html; Stuart Newman, *Deceptive Labeling of a Radical Embryo Construction Technique*, HUFFINGTON POST (Dec. 1, 2014),: http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html.

At the start of this initial period of consultation, forty one signatories including notable bioethicists, scholars, and scientists published a letter to the editor of *The Times* expressing alarm over HFEA's proposal for MRT.[68] This letter noted the broad global consensus against germline interventions, stated MRT would "cross the Rubicon" and open the door to other germline modifications, and may pose unforeseen consequences.[69] The authors also noted the transnational implications and urged HFEA against acting alone, declaring the U.K. must consider its "international responsibilities."[70] Despite exceedingly clear widespread opposition and breach of longstanding international precedent against germline modifications, HFEA continued its deliberative process.

A. HFEA Review and U.K. Department of Health

In 2014, the HFEA published a Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception ("HFEA Review").[71] The HFEA Review referenced a provision from an amendment passed in 2008 that defined a "[permitted] egg or embryo" as one that has been altered through a technique designed to avoid the transmission of mitochondrial disease.[72] Unlike the indicated use under consideration in the United States, the regulation in the U.K. only pertains to MRT for the purpose of avoiding mitochondrial disease and the HFEA Review specifies it does not currently encompass treatment for infertility. The HFEA Review reflected a favorable option toward MRT, basing its presumptions on measuring low preliminary levels of carryover maternal mutant mtDNA, asserting the methods of MRT are

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[68] Letter to the Editor, *Alarm Over Genetic Control of Embryos*, THE TIMES (March 20, 2013), http://www.thetimes.co.U.K./tto/opinion/letters/article3717615.ece.
[69] *Id.*
[70] *Id.*
[71] HFEA Scientific Review, *supra* note 31.
[72] *Id.* at 10.

"efficient" and "reassuring."[73] The HFEA Review also characterized that existing animal models demonstrated "good progress"[74] and concluded "the evidence does not seem to suggest the techniques are unsafe."[75]

During this process, the U.K. Department of Health issued several reports and statements describing the process of MRT that strategically characterized the procedure in a manner to avoid scrutiny for the crossing the bright line prohibition against germline modifications.[76] First, the U.K. Department of Health conceded that MRT constituted a germline modification, but argued that it did not pose a genetic modification because there is not an agreed upon definition of what a genetic modification entails.[77] The U.K. Department of Health suggested modifying mtDNA and performing nuclear genome transfer does not alter the oocyte or embryo's genetic information, asserting mtDNA merely functions as batteries of the cell.[78] Second, the U.K. Department of Health extended this presumption by maintaining MRT would not contravene the Universal Declaration on the Human Genome and Human Rights' prohibition against germline interventions because it serves a therapeutic corrective purpose so it does not harm human

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[73] *Id.* at 14.
[74] *Id.* at 18-19.
[75] *Id.* at 4.
[76] Connor, *supra* note 67; *Mitochondrial Donation: A 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*, U.K. DEP'T OF HEALTH at 13-14 (Feb. 2014), https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.; *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*, U.K. DEP'T OF HEALTH at 15 (July 2014), https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.
[77] *Id.*
[78] *Id.*

dignity.[79] This bizarre twisting of terminology not only distorted the characterization of MRT to the public, but fueled scientifically incorrect descriptions in British media aimed at garnering public support.

The HFEA Review acknowledged the potential for complications pertaining to safety and efficacy, but unilaterally disregarded what the scientific community has described as numerous substantial barriers.[80] For example, the HFEA Review addressed differential segregation and maternal bottleneck that could result in increasing levels of heteroplasmy during the offspring's course of development in different tissues, and increasing levels of heteroplasmy through subsequent generations.[81] In response to this possibility, the HFEA Review responded "there is little evidence of this occurring."[82] Importantly, HFEA's evaluation is based on the premise that PGD testing of the blastocyst (cells in early stages of embryonic development) constitutes an accurate representation of both lifetime heteroplasmy in all subsequently developed tissues and health of the eventual offspring.[83]

The HFEA cited animal studies using macaque models where about half of the macaque embryos appeared to develop normally as evidence of "good progress" that MRT appeared to work.[84] In response to the half of embryos following MRT that did not develop correctly, HFEA disregarded these findings, asserting there may be "some differences in embryo development, but nothing has been found to raise concerns of safety."[85] The HFEA also noted the concern that there may be incompatibility arising from mixing mtDNA from two sources, but concluded

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[79] *Id.*
[80] *See generally* U.K. Correspondence, *supra* note 32; FDA Meeting, *supra* note 11.
[81] HFEA Scientific Review, *supra* note 31, at 26.
[82] *Id.*
[83] *Id.* at 13.
[84] *Id.* at 20.
[85] *Id.* at 20.

mixing two sources of mtDNA would not pose any complications to interaction with nDNA or cell function.[86] As support for its conclusion, HFEA observed that children from mixed race parents (one source of maternal mtDNA) do not exhibit higher percentages of mitochondrial disease.[87]

B. Public Comments in the U.K. Policymaking Process

During this process, the U.K. House of Commons Science and Technology Committee held a hearing on the scientific evidence for MRT and published written correspondence from numerous scientists, physicians, bioethicists, and other stakeholders.[88] Although a minority of comments lent support to HFEA's proposed direction and even asserted it would be unethical not to use MRT,[89] the majority of public comments fervently opposed MRT precisely based on unsettling and unresolved issues pertaining to evidence for its safety and efficacy.[90] A number of comments highlighted the unpredictability of differential segregation and maternal bottleneck, asserting that attempting to measure carryover of maternal mtDNA in the blastocyst via PGD was an ineffective and improper proxy for predicting long term levels of heteroplasmy and health outcomes.[91] Comments also opposed HFEA's characterization of animal models as successful, noting that the 52% of animal embryos that did not develop correctly demonstrated chromosomal abnormalities, and questioned whether these findings may result in unexamined differences in

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[86] *Id.* at 23, 28-31.
[87] *Id.*
[88] U.K. Correspondence, *supra* note 31.
[89] *Id.* at 7-8. Progress Educational Trust asserted there was prevailing support for HFEA's regulation to permit MRT rationalizing al medical treatment entails experimental results, and it would be unethical not to employ MRT.
[90] *Id.* at 23, 29, 33-49, 48, 73.
[91] *Id.* at 33-35, 50, 64-66.

the embryos that scientists proclaimed were developing normally.[92]

In addition to these responses, multiple comments disputed HFEA's conclusion pertaining to the compatibility of two sources of mtDNA and epigenetic effects resulting from transfer of the nuclear genome from one oocyte or embryo to another.[93] A number of interested parties, including the Council for Responsible Genetics, Human Genetics Alert, and several scientific experts submitted similar assessments noting evidence for extensive communication between mtDNA and nDNA expression.[94] Disrupting mtDNA functioning and cross-talk to nDNA directly influences DNA methylation and chromosomal gene expression.[95] That is, mitochondria are not merely batteries supplying energy to the cell that can be deftly exchanged, but part of a complex interwoven system necessary for the entire organism's subsequent development.[96] These observations also highlighted the unprecedented risks related to embryo manipulation, noting the more extreme the level of physical manipulation, the higher the potential for physical damage to the embryo or epigenetic changes resulting from the process of physical manipulation and the risk for functional and developmental health deficits.[97]

Notably, these comments independently evaluated the status of scientific evidence underlying HFEA's conclusion that the techniques appear "not unsafe" and concluded the

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[92] *Id.* at 23; *see also* Aditi Shah, *"Not Unsafe" Does Not Equal Safe: An Evaluation of the HFEA's Report on MST and PNT*, COUNCIL FOR RESPONSIBLE GENETICS (June 3, 2014), http://www.councilforresponsiblegenetics.org/pageDocuments/Q2M4IDTBFZ.pdf [hereinafter "Council for Responsible Genetics"].

[93] U.K. Correspondence, *supra* note 31, at 29, 33-35, 39-49, 53, 64-65, 73.

[94] *Id.* at 33-35, 39-49; Council for Responsible Genetics, *supra* note 92; Human Genetics Alert, *supra* note 28; *Report on the Safety of "Mitochondrial Replacement" Techniques: Epigenetic Issues*, HUMAN GENETICS ALERT (March 2013), http://www.hgalert.org/Report%20on%20the%20safety%20of%20mitochondrial%20transfer.pdf .

[95] *Id.*

[96] *Id.*

[97] *Id.*

opposite: *these techniques are likely to be unsafe*.[98] Human Genetics Alert questioned why HFEA would blatantly dismiss substantial categories of potential risks, alleging its process was based on "disastrously flawed scientific assumptions," charged that the public consultation process was "biased" because HFEA did not accurately describe MRT, and asserted the amendment lacked public support.[99] Cell biologist Professor Stuart Newman reiterated Human Genetics Alert's objection to improper framing to the public because HFEA the technology as "mitochondrial donation." [100] Newman implored HFEA to appropriately label the technology as nuclear genome transfer, pointing out this technique creates a child through an evolutionary unprecedented experiment because it removes 20,000 chromosomes from one ooctye or embryo and transfer this nDNA into another oocyte or embryo.[101] Critics exhorted that "harmful consequences of these methods could impair entire generations," and issued proclamations that HFEA's conclusions were both "incomplete and unsubstantiated."[102] Reiterating this warning, cell biologist Professor Paul Knoeplfer proclaimed the U.K. was on the verge of an "historic mistake."[103]

C. The Role of British Media

The press quickly rebounded and parroted the U.K. Department of Health and HFEA's strategic framing to garner support for the 2015 amendment to the Human Fertilisation and

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[98] U.K. Correspondence, *supra* note 31, at 29, 48.
[99] *Id.* at 48.
[100] *Id.* at 73.
[101] *Id.* at 74.
[102] Council for Responsible Genetics, *supra* note 92, at 17; Reinhardt et al., *supra* note 17.
[103] Sarah Knapton, *Three Parent Babies Could Be At Greater Risk of Cancer, Warn Scientists*, THE TELEGRAPH (Feb. 3, 2015), http://www.telegraph.co.U.K./news/science/science-news/11385370/Three-parent-babies-could-be-at-greater-risk-of-cancer-warn-scientists.html.

Embryology Act that would expressly regulate MRT.[104] Professor Julian Savulescu compared MRT to a "micro-organ transplantation," alleging there is "no sound basis to oppose MRT" because it constitutes a "cure" so infants can be born without mitochondrial disease.[105] An article in the *Guardian* appealed to the pathos of parental suffering touting MRT as a method to prevent incurable genetic disease and "[save] families needless misery" over ill-advised objections of religious groups.[106] Both Savulescu and an article in the *New York Times* chided opposition to MRT, scoffing that "preventing medical advancement" is so illogical, it could only be based on being improperly informed.[107]

These pieces in the media not only reinforced incorrect scientific characterizations set forth by the U.K. Department of Health and the HFEA, but employed a dangerous precedent of classifying legitimate scientific dissent supported by credible evidence outside the parameters of acceptable discussion. Elevating the U.K. Department of Health and HFEA's presumptions as sacrosanct is not only scientifically disingenuous, but dangerous to the honesty and transparency required in the policymaking process.

D. Outcome of the U.K. Policymaking Process and Lessons for the U.S.

In November of 2016, HFEA recommended "cautious use" of MRT subject to a set of

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[104] Polly Toynbee, *This Isn't About Three-Parent Babies. Its About Saving Families Needless Misery*, THE GUARDIAN (Feb. 3. 2015), https://www.theguardian.com/commentisfree/2015/feb/03/three-parent-babies-families-religious-mps-vote-mitochondrial-replacement; Julian Savulescu, *Mitochondrial Disease Kills 150 Children a Year. A Micro-Transplant Can Cure It*, THE GUARDIAN (Feb. 2, 2015), https://www.theguardian.com/science/2015/feb/02/mitochondrial-transfer-micro-transplant-parliamentary-debate; Kenan Malik, *The Three-Parent Baby's First Step,* NEW YORK TIMES (Feb. 22, 2015), https://www.nytimes.com/2015/02/23/opinion/the-three-parent-babys-first-step.html.

[105] Savulescu, *supra* note 104.

[106] Toynbee, *supra* note 104.

[107] Savulescu, *supra* note 104; Malik, *supra* note 104.

conditions where individual fertility clinics must apply for a license to conduct the procedure.[108] Following HFEA's decision, the Newcastle Fertility Center announced its intent to submit an application for a license and begin the process of offering MRT to its fertility patients meeting the criteria set forth by HFEA.[109]

A number of key points emerged during the lengthy policymaking process in the U.K. that provides perspective when considering the process in the U.S. When HFEA and the U.K. Department of Health initially raised the possibility of MRT, bioethicists, scholars, and scientists noted MRT would breach the broad global consensus against germline modifications and urged the government to reconsider. To initially gain favor, the HFEA and the U.K. Department of Health strategically named the techniques MRT rather than accurately describing it as nuclear genome transfer. Relabeling a procedure by comparing it to an acceptable practice such as organ donation or replacing batteries obfuscated the gravity and risk involved. During the consultation process, numerous scientists provided testimony and correspondence at length relating to safety and efficacy. These scientists objected to HFEA's conclusions based on available evidence, finding not merely a lack of consensus pertaining to safety and efficacy, but that the available scientific evidence demonstrated how unsafe MRT is. Despite objections based on international governance, evidence demonstrating insufficient safety and efficacy, and lack of public consensus, British Parliament passed the amendment that would permit HFEA to license fertility

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[108] U.K.'s Independent Expert Panel Recommends "Cautious Adoption of Mitochondrial Donation in Treatment, HUM. FERTILISATION AND EMBRYOLOGY AUTH. (Nov. 30, 2016), http://www.hfea.gov.U.K./10559.html.

[109] Ian Sample, *U.K. Doctors To Seek Permission to Create Baby With DNA From Three People*, THE GUARDIAN (Nov. 30, 2016), https://www.theguardian.com/science/2016/nov/30/U.K.-doctors-to-seek-permission-to-create-baby-with-dna-from-three-people-mitochondrial-replacement-therapy; Ian Sample, *First U.K. Baby From Three People Could Be Born Next Year*, THE GUARDIAN (Dec. 30, 2016), https://www.theguardian.com/science/2016/dec/15/three-parent-embryos-regulator-gives-green-light-to-U.K.-clinics.

clinics to offer MRT reflecting a massive disconnect in the legal, scientific, and policymaking process.

V. United States Governance and Policymaking Related to MRT

Similar to the United Kingdom, the United States has undertaken steps to begin the process of permitting MRT. There is currently no legal prohibition against germline modification in the United States.[110] In 2014, the FDA convened meetings to discuss the medical rationale and scientific evidence pertaining to MRT for both the prevention of mitochondrial disease and the treatment of infertility.[111] In 2015, the White House announced that germline modifications constituted a line "that should not be crossed at this time"[112] and the NIH issued a statement it would not fund research involving germline modification.[113] However, in 2016, the National Academies of Science, Engineering, and Medicine issued a report (NAS Report) on the ethical and policy implications of MRT and concluded it is ethically permissible to conduct clinical investigations subject to a set of conditions.[114] Based on another subsequent report issued by NAS endorsing therapeutic germline modification through gene editing, it appears likely that the governance climate in the U.S. favors MRT, and any present prohibitions related to federal funding may potentially be lifted in the future.[115]

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[110] *See supra* notes 11-16.
[111] FDA Meeting, *supra* note 11; FDA Brief, *supra* note 13.
[112] *A Note on Genome Editing*, THE WHITE HOUSE (May 26, 2015), https://obamawhitehouse.archives.gov/blog/2015/05/26/note-genome-editing.
[113] Xavier Symons, *Interview: Carrie D. Wolinetz of the NIH on Gene Editing*, BIOEDGE (Feb. 23, 2016), https://www.bioedge.org/bioethics/interview-carrie-d.-wolinetz-of-the-nih-on-gene-editing/11770.
[114] NAS Report, *supra* note 13.
[115] *Human Genome Editing: Science, Ethics, and Governance*, NAT'L ACAD. OF SCI., ENG'G, & MED. (2017), https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance. The Dickey-Wicker Amendment prohibiting federal funding of research on human embryos contains an exception that permits research where the research would provide medical benefit to the embryo. *See* NAS Report, *supra* note 13, at 64.

A. Applicable FDA Regulations to MRT

In the United States, any clinical investigational use of MRT falls under the purview of the FDA. Under the Public Health Service Act ("PHSA"), the FDA regulates human cell and tissue products ("HCT/Ps"), which refers to articles "containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[116] These regulations are designed to prevent contamination and communicable disease rather than to ensure safety and efficacy.[117] They impose several requirements such as registering the HCT/Ps with the FDA and promulgating standards for Good Tissue Practices, including monitoring the procedures, facilities, processing equipment, and supplies and reagents used in the manufacturing process.[118] Under the HCT/P system set forth in 21 CFR §1271, the FDA classifies different types of human cells, tissues, and cellular and tissue-based products into categories for regulation based on the public health risks they pose: (1) products not subject to HCT/P regulations, (2) HCT/Ps regulated under Section 361 of the PHSA, and (3) products posing the most risk that are to be regulated stringently as a biological product or drug.[119]

In the late 1990s and early 2000s several clinics began to conduct cytoplasm transfers. These procedures differed from MRT currently under consideration because the procedure involved injecting cytoplasm from a donor containing mitochondria into the mother's oocyte and did not involve nuclear genome transfer.[120] Though technically distinct, these procedures

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[116] 21 C.F.R. § 1271.3(d) (2016).
[117] 21 C.F.R. § 1271.145 (2016).
[118] 21 C.F.R. § 1271.150 (2016).
[119] *Id.*; 21 C.F.R. § 1271.151 (2016).
[120] Carol A. Brenner et al., *Mitochondrial DNA Heteroplasmy After Human Ooplasmic Transplantation*, 74 FERTILITY & STERILITY 573 (2000); Serena Chen et al., *A Limited Survey-Based Uncontrolled Follow-Up of Study of Children Born After Ooplasmic Transplantation in a Single Centre*, 33 REPROD. BIOMEDICINE ONLINE 737 (2016); *see also* Castro, *supra* note 13, at 731.

resulted in the birth of seventeen children, two of whom had chromosomal abnormalities and one whom had with pervasive developmental disorder.[121] Only cursory follow-up has been conducted on the health of the resulting children, but the incident prompted the FDA to assert its jurisdiction over this area of reproductive technology.[122]

In 2001, the FDA expanded its definition of "human cells, tissues, or cellular or tissue based products" HCT/Ps to include semen or other reproductive tissue.[123] This required fertility clinics handling gametes and reproductive tissue to comply with requirements for laboratory registration, minimal procedures to screen HCT/Ps for communicable disease, and good manufacturing procedures.[124] FDA considers standard procedures such as IVF "minimal manipulation" and subject only to the requirements set forth in Section 1271.[125]

Around this time in 2001, the FDA sent a warning letter to the scientists conducting cytoplasm transfers, asserting clinical research involving the transfer of genetic material must be conducted pursuant to an investigational new drug application.[126] In 2009, the FDA issued guidance affirming this position, asserting procedures currently used for MRT including

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[121] *Id.*

[122] The subsequent health of the children was assessed using self-reported parent questionnaires but did not rely on physical medical testing. *See* Brenner et al., *supra* note 120; Chen et al., *supra* note 120; Castro, *supra* note 13, at 730-731; *Warning Letter, Letter to Sponsors/Researchers- Human Cells Used in Therapy Involving the Transfer of Genetic Material By Means Other Than the Union of Gamete Nuclei*, FDA (July 2, 2001), https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm [hereinafter "Ooplasm Warning Letter"].

[123] Evita Grant, *FDA Regulation of Clinical Applications of CRISPR-CAS Gene Editing Technology*, 71 FDA L. J. 608, 621 (2016); *What You Should Know: Reproductive Tissue Donation*, FDA, https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm232876.htm; FDA Meeting, *supra* note, at 14-17.

[124] *Id.*

[125] NAS Report, *supra* note, at 22.

[126] *Id.*; Ooplasm Warning Letter, *supra* note 122.

maternal spindle transfer and pronuclear transfer that involve the transfer of genetic material constitute "more than minimal manipulation" and require the investigator to submit an investigational new drug application.[127] Thus, clinical investigation of MRT would require "submitting preclinical data and information on product safety, details about technique, and proposed clinical investigation protocols" pursuant to an investigational new drug application.[128] If the FDA were to approve MRT and license its use for only one indication such as the prevention of mtDNA disease, clinics would be able to expand the scope of indications through off label use for other uses such as infertility and therapeutic energetic correction.[129] As with other drugs and biologics, off label use dramatically expands both the potential market and opportunity for commercial profit.

B. Federal Funding Considerations

In addition to federal regulations set forth by the FDA, clinical investigation using embryos would be subject to federal funding restrictions and subject to state laws pertaining to research on embryos, some of which appear to prohibit MRT.[130] At the federal level, the Dickey-Wicker Amendment prohibits the use of federal funds for research in which an embryo is created or destroyed.[131] However, some state laws as well the Dickey-Wicker Amendment contain exceptions in circumstances where the research on the embryo would provide benefit to the embryo or if the investigation is defined as therapeutic research designed to lead to gestation and birth of that embryo.[132] Finally, the Consolidated Appropriations Act of 2016 currently

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[127] FDA Meeting, *supra* note 11, at 15-17; *see* NAS Report, *supra* note 13, at 22.
[128] *Id.*
[129] NAS Report, *supra* note 13, at 68-69.
[130] *Id.* at 66-67.
[131] Grant, *supra* note 123, at 615.
[132] *See* NAS Report, *supra* note 13, at 59, 67.

prohibits the FDA from using federal funds to consider applications for an exemption for investigational use of a drug or biological product "in research in which a human embryo is intentionally created or modified to include heritable genetic modification."[133] Although the Consolidated Appropriations Act appears to prohibit the FDA from using federal funding to review applications for MRT, the NAS Report recently questioned whether MRT constitutes heritable germline modification, asserting it would require additional legal analysis which makes the application of the spending prohibition uncertain.[134]

C. FDA Meetings to Discuss Safety, Efficacy, and Risks of MRT

In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA held a meeting titled "Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility," ("MRT Meeting") which addressed the intersecting regulatory and scientific considerations pertaining to safety and efficacy of MRT based on available data and the state of scientific knowledge.[135] In conjunction with this meeting, the FDA published a briefing document ("MRT Brief") on the same summarizing the proposed methodology and areas of concern pertaining to safety.[136]

1. Determining Efficacy and Defining Success

During the MRT Meeting, the FDA addressed the patient population and indicators of how to define success. Significantly, the MRT Meeting not only addressed MRT for the prevention of mtDNA disease, but also for treating infertility. Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the

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[133] Section 749, Consolidated Appropriations Act, PUBLIC LAW NO. 114-113, 114th Congress (2015-2016); *see also* Castro, *supra* note 13, at 732.
[134] NAS Report, *supra* note 13, at 2.
[135] FDA Meeting, *supra* note 11.
[136] FDA Brief, *supra* note 13.

subject would be created using the proposed methodology. Past reports issued by the President's Council on Bioethics and the NAS have asserted that because the clinical investigation occurs on the embryo, it would not constitute human subjects research as defined in the Common Rule.[137] Under this interpretation, any research conducted prior to implantation need not meet the requirements set forth in the Common Rule such as its specific requirements for informed consent and the provision that the benefits must be greater than the risks as applied to the resulting child.

Participants at the MRT Meeting posed the question of how to define efficacy, with some participants proposing that efficacy can be determined from a viable pregnancy.[138] During the course of the meeting, however, commentators noted lack of scientific consensus pertaining to defining the parameters of efficacy, and some commentators urged testing the blastomere (cells in early stages of embryonic development) for viability is not indicative of the health of the child and subsequent offspring.[139] One scientist also noted that testing a sample is not indicative of the rest of the inner cell mass, meaning different levels of heteroplasmy may exist, and even subsequently develop at varied rates in different tissues though stages of development and the child's life.[140] Based on those metrics, efficacy could not be determined merely from a viable pregnancy but instead requires examining the health of the child and potentially the child's

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[137] NAS Report, *supra* note 13, at 92; "*Research Involving In Vitro Human Embryos,*" *Reproduction and Responsibility: The Regulation of New Biotechnologies*, THE PRESIDENT'S COMM. ON BIOETHICS at 164, 180 (2004), https://repository.library.georgetown.edu/bitstream/handle/10822/559381/_pcbe_final_reproduction_and_responsibility.pdf?sequence=1&isAllowed=y; *see also* Niklaus Evitt et al., *Human Germline CRISPR-CAS Modification: Toward a Regulatory Framework*, 15(12) AM. J. BIOETHICS 25 (2015).

[138] FDA Meeting, *supra* note 11, at 168, 246, 261-71.

[139] *Id.*

[140] *Id.* at 84-87, 85.

offspring. Scientists and scholars have commented on this bind, observing that we simply cannot know with certainty whether MRT would be safe and effective because germline intervention necessarily imposes substantial risk that cannot be eliminated.[141]

2. Current Barriers to Safety and Efficacy in MST and PNT

Throughout the course of the meeting, the participants discussed a number of barriers to safety and efficacy arising from mitochondrial biology described *supra* in Section II.

a. Maternal Bottleneck, Segregation, and Heteroplasmy

According to participants at the MRT Meeting, animal models have not sufficiently addressed maternal bottleneck, where levels of mutant mtDNA can increase from one generation to the next.[142] Currently, it is difficult to predict the child's pattern of inheritance based on the mother's percent of mutated mtDNA. Thus, a mother presenting without mtDNA disease based on her low level of heteroplasmy could give birth to a child with a high level of heteroplasmy that reaches the threshold to be affected by mtDNA disease. Furthermore, maternal bottleneck can increase the percent heteroplasmy in each subsequent generation.[143] A blastomere, or even a child that initially demonstrates low levels of heteroplasmy from mutant mtDNA carryover who appears healthy may pass on amplified risk to future generations who would present with mtDNA disease.[144] Some evidence exists to suggest these risks would particularly affect female generations.[145] These observations pertaining to maternal bottleneck mirror the shortcomings of PGD as a method of currently screening embryos at risk for mtDNA disease, and underscore the

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[141] Baylis, *supra* note, at 533; Lanphier et al., *Don't Edit the Human Germline*, 519 NATURE 410, 411 (2015) (Discussing the uncertainty of germline modifications, stating "The precise effects of genetic modification to an embryo may be impossible to know until after birth.").
[142] FDA Meeting, *supra* note 11, at 34-35, 141-142; FDA Brief, *supra* note 13, at 7, 21.
[143] *Id.*
[144] *Id.* at 132-35.
[145] FDA Brief, *supra* note 13, at 21, 39.

inability to predict efficacy based on testing the blastomere.[146] Additionally, even testing adult tissues may demonstrate no mtDNA mutations, but mtDNA mutations could be present in the germ cells of the individual and be passed on through reproduction to the subsequent generation, and increase from one generation to the next.[147]

Currently, effective methodology does not exist to account for testing the fluid mutations of mtDNA in every tissue over the human lifespan.[148] Following the procedure of MST or PNT, the combination of maternal mtDNA carried over into the donor oocyte continues to divide and increase in each cell of the growing organism. Biologist Dr. Shoukhrat Mitalipov, whose lab had been conducting investigations based on animal models, asserts segregation in tissues drifts toward homoplasmy, which would result in the donor's mtDNA dominance.[149] Despite Mitalipov's testimony at the MRT Meeting declaring favorable genetic drift, this presumption is not universally shared by other experts.[150] According to other research, there is little known about the dynamic by which mtDNA evolves within an organism, because one haplotype (the group of genes in mtDNA–here there is the maternal haplotype of mtDNA and the donor haplotype of mtDNA) could replicate faster than the other, which could result in a dramatic increase in the level of heteroplasmy.[151]

Segregation and replication of mtDNA occurs according to its own evolutionary system, which makes predicting subsequent levels of heteroplasmy difficult.[152] Even if segregation

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[146] *See* FDA Meeting, *supra* note 11, at 137; NAS Report, *supra* note 13, at 58.
[147] FDA Meeting, *supra* note 11, at 180, 239; NAS Report, *supra* note 13, at 58.
[148] FDA Meeting, *supra* note 11, at 180.
[149] *Id.* at 144.
[150] *See* U.K. Correspondence, *supra* note 32, at 33-35; Joerg Patrick Burgstaller et al., *mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated By Haplotype Difference and Developmental Stage*, 7 CELL REPORTS 2031, 2036 (2014).
[151] Burgstaller et al., *supra* note 150, at 2031.
[152] *Id.*

initially demonstrates favorable drift toward the donor's mtDNA, these levels may jump unpredictably, or segregate at different levels in tissues throughout the body.[153] Levels of mtDNA in the child's blood may reflect a low percent of heteroplasmy, but genetic drift can cause segregation toward the mother's mutated mtDNA in specific tissues or organs, wherein the child may experience diseases arising in those systems.[154] Specifically, one study demonstrated initial carryover rates of maternal mtDNA of 1.2% unexpectedly increased to 53% when studying embryos in culture, leading one biologist in favor of MRT to admit that "it would defeat the purpose of doing mitochondrial replacement" and "it is wise not to move forward with this uncertainty."[155] Finally, segregation occurs throughout the lifespan of the individual which means low levels of the mother's mtDNA in the child's blood or partial tissue testing would also not reflect the possibility of increasing levels of heteroplasmy later in life resulting in latent presentation of mitochondrial disease.[156] Thus, statements that claim heteroplasmy would not pose a problem if initial carryover of mtDNA appears unsupported by existing evidence.[157]

In addition to maternal bottleneck and segregation shifting the percent of mutant mtDNA, mutations in mtDNA that cause heteroplasmy naturally occur through aging and increases throughout one's life.[158] In addition to mutated mtDNA, both de novo (new) mutations and mutations to nDNA occur that can result in mitochondrial dysfunction.[159] Some scientists hypothesize there are naturally occurring levels in heteroplasmy in everyone contributing to

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[153] *Id.*; Ewen Callaway, *Three-Person Embryos May Not Expel Harmful Genes*, 533 NATURE 445 (2016).
[154] *Id.*
[155] Callaway, *supra* note 153.
[156] Burgstaller et al., *supra* note 150, at 2031.
[157] FDA Meeting, *supra* note, at 214-215, 222.
[158] *Id.* at 34-35.
[159] *Id.* at 194; FDA Brief, *supra* note 13, at 6.

common disease such as heart disease, diabetes, and neurodegeneration.[160] These mutations suggest two points: first, there are other factors influencing the evolution of mtDNA; and second, attempting to find a donor without mtDNA mutations would be difficult.[161]

b. Haplotype Incompatibility

Participants at the MRT Meeting also raised concerns relating to the potential for incompatibility arising from mixing two haplotypes of maternal mtDNA and donor mtDNA.[162] Although proponents of MRT state that haplotype mixing does not appear to result in abnormalities, these presumptions rest upon extrapolating projections that rely on two parent scenarios.[163] Some scientific evidence suggests that segregation appears affected by genetic distance between haplotypes and when haplotypes of maternal mtDNA and donor mtDNA are mixed, reversion toward maternal mtDNA occurs.[164] In animal models, mixed mtDNA has resulted in immune rejection, susceptibility to diseases of metabolism, and deficits in performance and learning capabilities.[165]

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[160] Joel Meyer et al., *Mitochondria as a Target of Environmental Toxicants*, 134 TOXICOLOGICAL SCI. 1, 3 (2013).
[161] FDA Meeting, *supra* note, at 66; *see also Letter from David Keefe, MD, to Anna Rajakumar, Human Fertilisation and Embryology Authority* (Mar. 24, 2014), http://www.biopoliticaltimes.org/downloads/DKeefeMRconsiderations.pdf.
[162] FDA Meeting, *supra* note 11, at 21, 42, 66; FDA Brief, *supra* note at 13, 14-15; NAS report, *supra* note 13, at 54-56.
[163] During the FDA MRT Meeting, proponent Dr. Dieter Egli dismissed concerns relating to haplotype mismatch, stating there is "good evidence" not to be concerned because the process of segregation (selection of one haplotype over another) is similar maternal inheritance of mtDNA to a son. Other proponents at the meeting repeated the presumption set forth during the U.K. discussions that analogized combining two maternal haplotypes in MRT to combining one maternal and one paternal haplotype during unassisted reproduction with interracial parents. *See* FDA Meeting, *supra* note 11, at 150-51, 213, 232-38.
[164] Burgstaller et al., *supra* note 150, at 2031; Eunju Kang et al., *Mitochondrial Replacement in Human Oocytes Carrying Pathogenic Mitochondrial Mutations*, 540 NATURE 270 (2016).
[165] FDA Meeting, *supra* note 11, at 196-187; Kimberly Dunham-Snary & Scott Ballinger, *Mitochondrial-nuclear DNA Mismatch Matters*, 349 SCIENCE 1449, 1550 (2015); Reinhardt et al., *supra* note 17, at 1345; Amato et al., *supra* note 19, at 34.

c. Cross-talk between mtDNA and nDNA

Contrary to the media representations that mtDNA's role is negligible except for unidirectional provision of energy, participants at the MRT meeting as well as substantial additional evidence demonstrate what scientists refer to as cross-talk, symbiosis, and co-evolution between mtDNA and nDNA.[166] Mitochondrial DNA not only provide energy, but control metabolic processes, programs cell growth and apoptosis, and impacts nDNA expression.[167] Scientists have described the interaction between mtDNA and nDNA as a complex evolutionary model, where the genome should be considered comparable to an ecosystem where every interconnected element affects the functioning of the whole.[168] Mitochondrial DNA not only functions as a source of energy, but affects a wide range of cellular functioning and how nDNA is expressed.[169] Disrupting the cross-talk between mtDNA and nDNA in animal models results in adverse outcomes and disturbs crucial mitochondrial processes.[170] Current research suggests interference in the communication between mtDNA and nDNA can negatively affect individual development, behavior, susceptibility to disease, and

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[166] *See generally* FDA Meeting, *supra* note, at 194; FDA Brief, *supra* note at 13, 18; Dunham-Snary & Ballinger, *supra* note 165; Reinhardt et al., *supra* note 17, at 1346; Martin Horan et al., *From Evolutionary Bystander to Master Manipulator: The Emerging Roles for the Mitochondrial Genome As A Modulator of Nuclear Gene Expression*, 21 EUR. J. OF HUM. GENETICS 1335 (2013); Rebecca Muir et al., *Mitochondrial Content Is Central To Nuclear Genome Expression: Profound Implications for Human Health*, 38 BIOESSAYS 150 (2015).
[167] FDA Brief, *supra* note, at 5; Claiborne et al., *supra* note 16; Dunham-Snary & Ballinger, *supra* note 165; Eli Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832 (2016).
[168] Human Genetic Alert, *supra* note 94, at 4; Reinhardt et al., *supra* note 17, at 1346; Nathaniel Comfort, *Can We Cure Disease Without Slipping Into Eugenics?* THE NATION (July 16, 2015), https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/.
[169] FDA Brief, *supra* note 13, at 13
[170] NAS Report, *supra* note 13, at 56.

fertility.[171] As one scientific article summarized, "perturbation of the mito-nuclear interactions . . . generally attracts grave consequences."[172]

d. Animal and In Vitro Models

Based on the current knowledge of animal models, participants at the MRT Meeting raised the same concerns as in the U.K. discussions about characterizing the current evidence and limitations of current studies.[173] Proponents have highlighted animal models using a small population of macaques, finding low initial percentages of heteroplasmy and declaring "positive results" that the offspring are "healthy."[174] However, participants at the MRT meeting noted several shortcomings: those studies relied on a small sample and may miss problems that would arise with a larger sample; they did not perform extensive testing for heteroplasmy throughout tissues; the studies did not test germ cells for heteroplasmy or assess the health of subsequent generations; and cautioned that using sample tests for heteroplasmy as a proxy for health may miss other dysfunction.[175]

In vitro studies evaluating the development of embryos appeared to raise similar concerns from participants at the MRT Meeting.[176] According to Dr. Paula Amato and colleagues, some studies demonstrated 50% reduced embryo development following PNT, higher rates of

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[171] Human Genetic Alert, *supra* note 94, at 4; Reinhardt et al., *supra* note 17, at 1346; *see also* Horan et al., *supra* note 166, at 1335-1336; Muir et al., *supra* note 166, at 152-153; Dunham-Snary & Ballinger, *supra* note 165.
[172] Horan et al., *supra* note 166, at 1335.
[173] Amato et al., *supra* note 19, at 32; Fogleman et al., *supra* note 35; FDA Meeting, *supra* note 11, at 134, 251.
[174] *Id. See also* Adashi & Cohen, *supra* note 167, at 833.
[175] FDA Meeting, *supra* note 11, at 185, 251; Dunham-Snary & Ballinger, *supra* note 165, at 250.
[176] FDA Meeting, *supra* note 11, at 203; Shah, *supra* note 92, at 8; Human Genetic Alert, *supra* note 94, at 5.

abnormal fertilization, and aberrant chromosomal segregation.[177] Despite these findings, Dr. Amato and colleagues presume that the development of the remaining embryos signals viability and health.[178] Participants at MRT Meeting disagreed, and instead suggested the remaining embryos that survive may also be affected with developmental shortcomings.[179] These findings have led Dr. David King of Human Genetics Alert to conclude the embryos that do survive may develop subtle latent deficits, and has asserted that presuming the opposite– that embryo survival equates to safety and efficacy– seems risky.[180]

3. Risks Arising from Assisted Reproductive Technology, Oocyte Manipulation, and Epigenetic Impact

In addition facing unpredictability and uncertainty arising from mitochondrial biology, the participants at the MRT Meeting and additional research have examined background risks arising from using assisted reproductive technology ("ART"), risks from the process and procedures involved with MRT, and epigenetic impact on the health of the child.

Numerous studies have assessed the impact of "considerable epigenetic changes" on the health outcomes of children born through the process of ART.[181] According to some figures, children born through ART have a 30-40% increased rate of major congenital malformations,[182]

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[177] Amato et al, *supra* note 19, at 33.
[178] *Id.*
[179] FDA Meeting, *supra* note 11, at 203; *see also* Human Genetics Alert, *supra* note 94, at 6.
[180] Human Genetics Alert, *supra* note 94, at 5.
[181] FDA Meeting, *supra* note 11, 91-92.
[182] Yue-hong Lu et al., *Long Term Follow-up of Children Conceived Through Assisted Reproductive Technology*, 14 BIOMEDICINE & BIOTECHNOLOGY 359, 361 (2013); Claudia Wallis, *Studies Link Infertility Treatments to Autism*, TIME (May 20, 2010), http://content.time.com/time/health/article/0,8599,1990567,00.htm; Jorien Seggers et al., *Congential Abnormalities in the Offspring of Subfertile Couples: A Registry Based-Study in the Northern Netherlands*, 103(4) FERTILITY & STERILITY 1001 (2015).

increased risk of autism,[183] more childhood illness,[184] a higher occurrence of cardiovascular conditions,[185] and an increased risk of cancer.[186]

Researchers have hypothesized a number of reasons for such outcomes, including drugs used by the mother during ovarian stimulation;[187] that impaired fertility may signal existing genetic mutations, in either mtDNA or nDNA, in the mother's oocytes;[188] and the impact of damage caused to the embryo arising from physical manipulation and the processes used during ART.[189] Current research suggests a correlation between the amount of physical manipulation to the embryo and level of damage resulting in potentially serious health deficits.[190] Physical damage may result from temperature shifts;[191] reagents used and time the embryo spends in culture;[192] destruction to cellular architecture;[193] and with MRT, potential for viral contamination based on a particular virus used during the procedures.[194] These factors could result in damage

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[183] Wallis, *supra* note 182.
[184] Lu et al., *supra* note 182.
[185] Maia Szalaviz, *The Link Between Infertility Treatments and Birth Defects*, TIME (May 7, 2012), http://healthland.time.com/2012/05/07/the-link-between-infertility-treatments-and-birth-defects/.
[186] E. Susan Amirian & Melissa Bondy, *Assisted Reproductive Technology and Risk of Cancer in Children*, 137 PEDIATRICS e20154509 (2016); Marte Reigstad el al., *Risk of Cancer in Children Conceived by Assisted Reproductive Technology*, 137 PEDIATRICS e20152061 (2016).
[187] FDA Meeting, *supra* note 11, at 77, 88; NAS Report, *supra* note 13, at 58.
[188] *Id.* at 87, 172; Anonymous, *Experts Warn of IVF Timebomb*, U.K. DAILY MAIL, http://www.dailymail.co.U.K./health/article-195627/Expert-warns-IVF-timebomb.html.
[189] FDA Meeting *supra* note 11, at 203, 232-233; NAS Report, *supra* note 13, at 58; FDA Brief, *supra* note 13, at 14-15, 20.
[190] Human Genetics Alert, *supra* note 28, at 4-5; U.K. Correspondence, *supra* note 32, at 39-49.
[191] FDA Brief, *supra* note 13, at 15.
[192] FDA Brief, *supra* note 13, at 20; NAS Report, *supra* note 13, at 58; FDA Meeting, *supra* note 11, at 104-105; Human Genetics Alert, *supra* note 94, at 3.
[193] FDA Brief, *supra* note 13, at 19; Human Genetics Alert, *supra* note 94, at 3; Human Genetics Alert, *supra* note, 28 at 5.
[194] Participants at the MRT Meeting discussed the use of the Sendai virus during MRT, citing it would be a potential viral contaminant because it may not be fully washed away following the procedure, and it may lie dormant and pose latent risks to children. *See* FDA Meeting, *supra* note 11, at 121-130; FDA Brief, *supra* note 11, at 19. The NAS Report also stated the Sendai

to cellular structure, aneuploidy, or disruption of chromosomal segregation and division.[195]

Some of the elements introduced during MRT such as temperature changes, use of reagents, and changing the composition of mitochondria through MST or PNT may have an epigenetic impact on the embryo and modify the expression of nDNA.[196] During discussions in both the U.K. and the U.S., participants described a critical window of vulnerability during which changes to the embryo will influence long term health outcomes through modifying gene expression.[197] These epigenetic changes could result in "imprinting or programming of future disease in children."[198]

During the closing statements by participants at the MRT Meeting, an overwhelming number of speakers voiced concern not only that scientific evidence failed to demonstrate safety and efficacy, but that MRT may never be a viable option based on level of risk involved.[199] Participants reiterated there are less risky alternatives to having children, and the current evidence falls "far short" of showing MRT would be potentially safe and effective.[200] Germline modification by its nature means MRT would pose unprecedented risks to the children born as a result.[201] MRT would impact every cell in the body, and there are no methodologies currently to

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virus has the potential for immunogenicity and poses unknown risks to children born using the virus during the procedure. NAS Report, *supra* note 13, at 38; *see also* Letter from David Keefe, *supra* note 161.

[195] FDA Brief, *supra* note 13, at 19.

[196] *See* NAS Report, *supra* note 13, at 58; FDA Meeting, *supra* note 11, at 95-98, 276; Muir et al. *supra* note 166, at 151; Human Genetics Alert, *supra* note 94, at 1, 3.

[197] FDA Meeting, *supra* note 11, at 96; U.K. Correspondence, *supra* note 32, at 39-49.

[198] The participants at the FDA Meeting discussed fetal origins of disease, where factors in the mother's environment such as nutrition and stress have a dramatic impact on the subsequent development of the child's risk for disease. *See* FDA Meeting, *supra* note 11, at 95-98.

[199] FDA Meeting, *supra* note 11, at 248, 261-271.

[200] *Id.*

[201] Mark Frankel, *Inheritable Genetic Modification and a Brave New World: Did Huxley Have It Wrong?* 33HASTINGS CTR REP. 31, 32 (2003).

ensure the procedure would not inflict novel abnormalities. [202] Based on available research, scientists cannot currently predict lifetime safety nor latent effects.[203] Such mistakes are both inevitable and irreversible, which means MRT could potentially not only create a congenitally impaired child, but introduce those deficits into the germline of all subsequent offspring.[204] Indeed, current research suggests disrupting mtDNA through MRT may have the potential to result in developmental disorders,[205] latent fatalities,[206] expedited aging,[207] increased risk of cancer,[208] as well as unknown abnormalities.[209] The weight of the evidence unquestionably points not merely to insufficient evidence of safety and efficacy, but should raise utmost alarm for the severity of potentially imposing novel risks. These extensive considerations do not support the National Academies of Science, Engineering, and Medicine Report's conclusion that conducting clinical trials for MRT is ethically permissible.

D. NAS Report on the Ethical Permissibility of MRT

Following the FDA's MRT Meeting and MRT Brief that cited numerous risks and lack of evidence pertaining to safety and efficacy, the FDA requested that the National Academies of Science, Engineering and Medicine develop a consensus report reviewing the ethical, social, and policy considerations relating to MRT.[210] The NAS Report concluded it is ethically permissible for the FDA to conduct clinical investigations subject to a set of conditions including: (1) Initial

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[202] FDA Meeting, *supra* note 11, at 278.
[203] *Id.* at 220.
[204] Zaret, *supra* note 54, at 1816; FDA Brief, *supra* note 13, at 22.
[205] Knapton, *supra* note 103.
[206] Burgstaller et al., *supra* note 150.
[207] Horan et al., *supra* note 166.
[208] *Id.*
[209] *See also* FDA Meeting, *supra* note 11, at 216 (discussing list of potential risks) and at 278 (discussing the potential for introducing additional abnormalities through MRT).
[210] NAS Report, *supra* note13, at xiii.

safety is established and risks to all parties directly involved in the proposed clinical investigations are minimized; (2) Likelihood of efficacy is established by preclinical research; (3) Clinical investigations are limited to women who otherwise are at risk of transmitting a serious mtDNA disease; (4) Intrauterine transfer for gestation is initially limited to male embryos (but may be extended to females if safe and effective); (5) FDA may consider haplotype matching as a means of mitigating risk of incompatibilities between mtDNA and nDNA.[211]

The NAS Report stated its goals are to minimize risks to the future child and ensure safety and efficacy of clinical interventions.[212] Despite setting forth this goal, the substance of the NAS Report discussion focused on prioritizing novel technological interventions as a means to advance science and medicine, asserting the FDA should exercise caution but not impose absolute limits on technology.[213] Echoing the position set forth in British media, the NAS Report maintained that opposition to MRT arises out of unfounded fear, poor understanding of the science, and an irrational belief that "natural" is necessarily better.[214] According to the NAS Report, parents take steps daily to improve their children through education and using medicine when children are ill, and categorized MRT as another option for parents to choose on behalf of their children's health and well-being.

However, comparing providing an existing child with a proper education against undertaking an unprecedented experiment to create a child with known risks that contravenes multiple global legal prohibitions are incommensurate actions. By refusing any absolute limits, the NAS Report necessarily weighs the scale in favor of finding benefit in the sake of pursing

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[211] *Id.* at 10-11.
[212] *Id.* at 2.
[213] *Id.* at 7.
[214] *Id.* at 89.

research for its own sake even when serious reservations of safety and efficacy exist. At times, the notion of progress requires a prudent pause and adherence to limits where technology would pose grave risk of harm to the intended recipient.

The NAS Report also justified the use of MRT based on longstanding jurisprudence respecting parental autonomy and procreative liberty.[215] In the history of ART, the desire to bear genetically related children has been prized, and parents have traditionally been provided wide lenience to pursue their "reproductive projects."[216] However, a number of bioethicists have observed this right need not be absolute nor demand all technology available without regard to whether the original conception of procreative liberty even encompasses such a right, or how exercising that right would impinge upon the rights of the child.[217]

In a similar manner as the U.K., the NAS Report employed linguistic creativity, asserting that although MRT is germline modification, it is not heritable because initial transfer for gestation would be limited to males who would not pass on mtDNA to their children.[218] Throughout the NAS Report the NAS took great care to minimize the role of mtDNA, reassuring that MRT does not "edit genes" and "there is no direct modification of mtDNA"[219] because MRT merely replaces pathogenic mtDNA with unaffected mtDNA.[220] Designed to minimize the impact of MRT as heritable germline modification, this statement is scientifically inaccurate and

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[215] *Id.* at 82-83.
[216] *Id.* at 82-83, 87; Baylis, *supra* note 29, at 533; Leon Kass, *Life, Liberty, and the Defense of Dignity* (2002).
[217] Baylis, *supra* note 29, at 533; Kass, *supra* note 216, at 163-164. Kass asserts: "When the exercise of a previously innocuous freedom now involves or impinges on troublesome practices the original freedom was never intended to encompass the general presumption of liberty needs to be reconsidered."
[218] NAS Report, *supra* note 13, at 29.
[219] *Id.* at 6-8.
[220] *Id.* at 107-108.

perpetuates misunderstanding. The description minimizing the actual procedure of a nuclear genome transfer by describing it as switching mitochondria echoes the misleading descriptions provide by the HFEA and the U.K. Department of Health. Furthermore, all germline modifications are heritable because changes to the oocyte or embryo globally impact all the resulting cells, impacting the growth and development of the child and the expression of nDNA, which is passed on by both males and females.[221] This attempt at extricating MRT from the category of heritable modifications is likely both a move to slowly introduce the concept of germline modification as well as a carefully executed strategy to assert that current limitations prohibiting federal funding for heritable germline modifications would not apply to MRT.[222]

Finally, the NAS Report addressed international treaties and global prohibitions against germline modification.[223] According to the NAS Report, the language set forth in the United Nations Universal Declaration on the Human Genome and Human Rights declaring that the genome constitutes "the heritage of humanity" amounts to "vague and aspirational" language, and the NAS is "not persuaded that MRT should be prohibited based on arguments that the genome represents the inviolable heritage of humanity."[224] The NAS Report's blatant disregard for conclusive positions set forth by the United Nations along with persuasive nonbinding precedent set forth by the Council of Europe entails the very action cautioned by the UNESCO's International Bioethics Committee when it warned of parsing component parts of the genome,

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[221] Frankel, *supra* note 201, at 32.
[222] Sec. 749, Consolidated Appropriations Act, *supra* note 133. The Omnibus Spending Bill "Prohibits the FDA from acknowledging applications for an exemption for investigational use of a drug or biological product in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Provides that any submission is deemed not to have been received, and the exemption may not go into effect." *See also* NAS Report, *supra* note 13, at 65.
[223] NAS Report, *supra* note 13, at 63, 89.
[224] *Id.* at 93.

renouncing limitations, and permitting market forces to stretch the boundaries of permissible endeavors. Furthermore, the position of UNSECO's International Bioethics Committee, the Council of Europe, and criminal prohibitions on germline modification set forth by numerous nations demonstrates the United Nations' language constitutes an unwavering and unmistakable directive rather than "vague and aspirational language."

VI. Additional Scientific and Ethical Considerations

After reviewing the scientific elements pertaining to safety, efficacy, and risks at the FDA MRT Meeting and the ethical, social, and policy issues contained in the NAS Report, these discussions omitted significant additional considerations. First, permitting clinical investigation of MRT and announcing the ethical acceptability of MRT relies upon expanding the pool of oocyte donors. Second, discussions at the FDA and in the NAS Report accept proponent's medical rationale for MRT for uses such as to treat mitochondrial disease and infertility without substantive analysis. Each of these points warrants further discussion to consider how clinical investigation would impact crucial parties involved in the process–potentially a new pool of egg donors, and whether available evidence supports the findings that MRT constitutes an effective method to treat mitochondrial disease and infertility.

A. Increasing Oocyte Donation and Risks to Donors

Although limited literature in the area addresses the impact of permitting MRT on oocyte donors and increasing risk in the pool potential oocyte donors, these considerations were not mentioned during the FDA MRT Meeting nor in the NAS Report.[225] MRT not only poses significant risks to the child, but because it relies upon oocyte donation, it would require increasing the number of oocyte donors and compound the current ethical debates pertaining to

[225] *See* Baylis, *supra* note 29, at 532; Fogleman et al., *supra* note 35, at 46.

the acceptability of risk and conflicts of interest present in this sector of the fertility industry.[226] Although some scholars reason autonomy and informed consent obviate ethical hesitation, this conclusion deserves further investigation.[227]

Every year, millions of women donate oocytes and are generally paid $5,000-$20,000 per cycle.[228] The process of egg donation requires multiple steps, beginning with a medical screening questionnaire and blood tests to check for infectious disease. If the fertility clinic selects this egg donor, then the clinic will begin the process of coordinating the donor's hormonal cycle with the intended mother's by starting a ten to twenty one day cycle of a hormone such as Lupron to suppress ovulation followed by a seven to twelve day regimen of injections of high doses of follicular stimulating hormones.[229] When the donor's oocytes have matured, the fertility clinic administers a final injection of human chorionic gonadotropin. After the injection of human chorionic gonadotropin, the donor undergoes surgery with anesthesia, where the physician inserts a needle through her vagina to remove the eggs that were produced.[230] Unlike a normal monthly cycle that produces one egg, this procedure generally produces around ten to twenty eggs or more depending on the amount of fertility drugs the clinic uses.[231]

The process of egg donation exposes donors to a number of short term physical risks in

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[226] *See generally* Justine Durrell, *Women's Eggs: Exceptional Endings*, 22 HASTINGS WOMEN'S L. J., 187 (2011); Joseph Gregorio, *Hatching A Plan Toward Comprehensive Regulation in Egg Donation*, 65 DEPAUL L. REV. 1283 (2016); Lisa Ikemoto, *Reproductive Tourism: Equality Concerns in the Global Market for Fertility Services*, 27 LAW & INEQUALITY 277 (2009).
[227] *See* Fogleman et al., *supra* note 35, at 46.
[228] Gregorio, *supra* note 226, at 1285-86.
[229] *Id.* at 1288-1290; Durrell, *supra* note 226, at 192-94.
[230] *Id.*
[231] *Id.* Some clinics report retrieving up to forty eggs in one cycle compared to the one egg naturally released per cycle.

connection to the fertility drugs used and the surgical process of retrieving the eggs. Adverse effects from the hormone injections may include pain, nausea, hot flashes, mood swings, hair loss, depression, bone pain, chronic enlargement of the thyroid, liver dysfunction, and heavy bleeding.[232] Ironically, evidence also suggests hormone injections of Lupron, a drug to suppress ovulation commonly during the process of syncing the donor's cycle to the mother's, can lead to the donor's own infertility because it may disrupt long term ovarian function in the donor.[233] Drugs used during this process can also result in ovarian torsion, where the ovaries change position from the drug induced stimulation in a manner that blocks blood flow and twists the ovary.[234] This condition requires medical intervention to remediate and may result in loss of ovarian function or surgical removal of the ovary.[235] The surgical process of egg retrieval carries risks associated with general surgery such as danger of infection, complications from anesthesia, and hemorrhage, as well risks related to the process of egg retrieval such as injury to adjacent areas like the ureter, bladder, or bowel.[236]

Donors may also experience ovarian hyperstimulation syndrome ("OHSS"), which is

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[232] Fogleman et al., *supra* note 35, at 46; Durrell, *supra* note 226, at 195-198; Gregorio, *supra* note 226, at 1291; Danielle Vera, *R-egg-Ulation: A Call for Greater Regulation of the Big Business of Human Egg Harvesting*, 23 MICH. J. GENDER & L. 391, 397 (2016).
[233] *Id. See also* Amicus Curiae, Karin Klein v. TAP Pharmaceutical Products, Inc. and Abbott Laboratories, 11-CV-17250 at 13 (2013), http://www.lupronvictimshub.com/lawsuits/Klein_Amicus_Published.pdf. Dr. David Redwine accessed Tap Pharmaceutical's raw data from clinical trials for Lupron and found data to suggest sixty-five percent of women who used Lupron did not return to their baseline ovarian function and the data suggested Lupron induced long term ovarian damage; Donna de la Cruz, *Should Young Women Sell Their Eggs?* NEW YORK TIMES (Oct. 20, 2016), https://www.nytimes.com/2016/10/20/well/family/young-women-egg-donors.html.
[234] Vera, *supra* note 232, at 397; Sandhya Krishnan et al., *Ovarian Torsion in Infertility Management- Missing the Diagnosis Means Losing the Ovary: A High Price to Pay*, 4 J. HUM. REPRO. SCI. 39 (2011).
[235] *Id.*
[236] Durrell, *supra* note 226, at 195.

fluid build-up in the abdomen and chest caused by gonadotropin stimulation of the ovaries.[237] Fluid leads to pressure on the diaphragm that causes difficulty breathing and decreases blood volume. In severe cases, OHSS can lead to kidney damage, blood clotting disorders, stroke, and death.[238] Estimates suggest the majority of women undergoing egg retrieval experience at least mild OHSS.[239] Although the fertility industry has stated complications from donation and OHSS are rare, such an assertion is not supported by available data.[240] Although fertility clinics keep statistics on pregnancy outcomes, they generally do not keep records on medical complications associated with the process of donating.[241] Recent independent research that studied the frequency of complications found varying rates of adverse events: approximately thirty percent of donors suffered OHSS, and between eleven and thirty percent of donors suffered complications so severe they required hospitalization.[242]

Despite the American Society for Reproductive Medicine's claim that there are no long term adverse risks of egg donation, this statement inaccurately represents both the known and unknown long terms risks associated with being an egg donor.[243] There are currently no registries tracking either short term or long term donor outcomes, so comprehensive data for all donors simply does not exist.[244] Despite lack of donor wide registries, numerous studies have

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[237] *Ovarian Hyperstimulation Syndrome*, AM. SOC'Y FOR REPROD. MED., https://www.asrm.org/FACTSHEET_Ovarian_Hyperstimulation_Syndrome/.
[238] *Id.* at 196-197.
[239] Vera, *supra* note 232, at 418-19.
[240] *Id.*
[241] Durrell, *supra* note 226, at 195.
[242] Vera, *supra* note 232, at 418-19.
[243] Sandra Boodman, *Do Women Who Donate Their Eggs Run A Health Risk?* WASHINGTON POST (June 20, 2016), https://www.washingtonpost.com/national/health-science/do-women-who-donate-their-eggs-run-a-health-risk/2016/06/20/8755b22e-1c7a-11e6-b6e0-c53b7ef63b45_story.html?utm_term=.699a554b5edb.
[244] *Id*; see *also* Durrell, *supra* note 226, at 219-20.

explored the link between different drugs used during the donation process and in numerous cases found an increased risk for a variety of cancers, including colon, breast, endometrial, uterine, ovarian cancer as well as malignant melanoma and non-Hodgkins lymphoma.[245] Donation may also result in long term compromise of the donor's own fertility, chronic pelvic pain and ovarian cysts.[246]

Critics of the current donation process have noted deficiencies arising from insufficient informed consent and conflicts of interest inherent in the egg donation process. Despite evidence demonstrating these short term and long term risks, donors may not even be aware of these risks when deciding to undergo donation.[247] One study found twenty percent of donors were not aware there were health risks involved, let alone serious complications such as OHSS, loss of her own fertility, and increased risk of cancer.[248] This discrepancy suggests serious deficiencies in the informed consent process.[249] Fertility clinics' metrics of success hinge upon successful pregnancies, which also creates an incentive for clinics to increase the dosage of fertility drugs to produce more eggs in one cycle.[250] Although higher doses of drugs will yield more eggs and benefit the clinic, it also places the egg donor at greater risk of adverse health consequences.[251]

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[245] Vera, *supra* note 232, at 395-96 (*citing* a thirty to forty percent increased risk for colon cancer); Durrell, *supra* note 226, at 200-02 (*citing* a 2.3-fold increase risk for ovarian cancer from Clomiphene, a three to four-fold increased risk for uterine cancer, an increase in breast cancer and malignant melanoma from Clomiphene use, and an increase in non-Hodgkins lymphoma); Gregorio, *supra* note 226, at 1291.
[246] Durrell, *supra* note 226, at 212.
[247] Boodman, *supra* note 243.
[248] *Id.*
[249] *Id.*
[250] Gregorio, *supra* note, at 1289-90.
[251] Sonia Suter, *Giving In To Baby Markets: Regulation Without Prohibition*, 16 MICH. J. GENDER & L. 217, 233, 254 (2009); Ikemoto, *supra* note 226, at 304-05 (observing "this normative dynamic creates an inverse relation between the donor's intrinsic worth and her extrinsic value in the fertility industry"); Hannah Devlin, *Increase In IVF Complications Raises Concerns Over Use of Fertility Drugs*, THE GUARDIAN (Nov. 13, 2016),

Legal scholars assert this creates a system that treats oocyte donors as separate and fungible producers of raw materials for a lucrative industry.[252] If the fertility industry would accurately disclose and assess risks, this would jeopardize donor willingness and undermine the supply of raw material upon which fertility clinics rely.[253] Discussions that euphemistically refer to "cytoplasm donors,"[254] and swapping out mitochondria obscures the fact that MRT relies on a supply of eggs that entails potentially serious risks to egg donors, of which they may not even be aware. Failing to address where the raw materials for MRT originated and focusing solely on risks to the child skews the risk-benefit ratio of this experimental procedure. Thus, even those who believe MRT in potential benefit to the child must also evaluate whether this benefit is justified at the expense of placing a pool of women's health at risk for the "reproductive projects" of third parties.[255]

B. Evaluating the Medical Rationale of Using MRT to Treat Mitochondrial Disease and Infertility

1. Sources of Mitochondrial Dysfunction

In addition to the risk profile for MRT, it is crucial to analyze whether MRT would effectively and sustainably address causes of mitochondrial dysfunction. As stated in Section II, dysfunction may result from either mtDNA mutations or nDNA mutations. Eighty percent of mitochondrial dysfunction arises from nDNA mutations for which MRT would not address. Mitochondrial DNA mutations may either be maternally inherited or arise de novo, as new

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https://www.theguardian.com/society/2016/nov/13/increase-in-serious-ivf-complications-raises-concerns-over-use-of-fertility-drugs-ovarian-hyperstimulation-syndrome.

[252] Ikemoto, *supra* note 226, at 285; Suter, *supra* note 251, at 224.

[253] *Id.*

[254] Fogleman et al, *supra* note 35.

[255] *See* Baylis, *supra* note 29, at 233.

mutations. Recent evidence suggests that a variety of environmental factors induce de novo mutations. Mitochondrial dysfunction is not only a cause of rare fatal disease, but also has been implicated as a factor in the development of common diseases, such as neurodegenerative disease, cancer, diabetes, cardiovascular disease.[256] Public health researchers hypothesize that the rising rates of chronic and debilitating disease are a product of environmentally mediated epigenetic damage to our mitochondria.[257] Changes in mitochondrial integrity appear to influence a number of diseases, more than the traditionally defined classes of maternally inheritance of mtDNA disease and nDNA mitochondrial disease.

Mitochondria undergo rapid development called mitochondrial biogenesis during embryonic and fetal development, and continue to replicate throughout one's lifetime. During this critical window of early development, altered maternal mitochondrial function directly impacts fetal development.[258] If mitochondria are damaged during these early stages, scientists believe the mtDNA deficiencies will continue to replicate during the growth of the organism.[259] Mitochondria undergo continual growth and repair throughout the life cycle of the organism, but if the cell's repair mechanisms cannot keep pace with external assaults that induce these changes, cumulative damage will eventually manifest phenotypically in a disease state.[260]

In the course of one's life mitochondria are "on the frontline of cellular response to the

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[256] Meyer, *supra* note 160, at 3.
[257] Luca Lambertini & Hyang-Min Byun, *Mitochondrial Epigenetics and Environmental Exposure*, 3 CURRENT ENVTL. HEALTH REP. 214 (2016).
[258] Kelly Brunst et al., *Integrating Mitochondriomics In Children's Environmental Health*, 35 J. APPLIED TOXICOLOGY 976 (2015).
[259] Meyer, *supra* note 160.
[260] *Id.* at 6; Maria Paraskevaidi et al., *Underlying Role in Mitochondrial Mutagenesis in the Pathogenesis of Disease and Current Approaches for Translational Research*, 32 MUTAGENESIS 335, 336 (2016).

environment."[261] Recent research demonstrates how environmental factors induce epigenetic changes in mitochondrial activity that can also lead to alternation in nDNA.[262] A variety of environmental agents, including pesticides,[263] heavy metals,[264] antibiotics,[265] pharmaceutical drugs,[266] environmental toxicants such as dioxin[267] and Bisphenol A[268] can all exert changes to mitochondrial integrity and development. Over time, exposure to mitochondrial disruptors damages the mitochondria and impacts the resulting health of the individual. As discussed in Section II, proper functioning of each cell and the organism as a whole relies on cross-talk between mtDNA and nDNA. Environmentally mediated mtDNA damage undermines bidirectional cross-talk and interferes with nDNA repair pathways, which can influence nDNA methylation and produce epigenetic changes in the expression of nDNA.[269] When accumulations of mtDNA damage and nDNA damage reaches a particular threshold, this manifests as common diseases.[270]

This research suggests that even presuming the initial procedure of MRT could ever be safe and effective, it would not address underlying causes of de novo mtDNA mutations nor de novo nDNA mutations that phenotypically present as disease. These findings have several implications for the long term safety and efficacy of MRT over the course of the child's life.

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[261] Lambertini & Byun, *supra* note 257.
[262] *Id.*
[263] Meyer, *supra* note 160, at 8; Paraskevaidi, *supra* note 260, at 1.
[264] *Id.*; Brunst, *supra* note 258, at 982-983.
[265] Sameer Kalghati et al., *Bactericidal Antibiotics Induce Mitochondria Dysfunction and Oxidative Damage in Mammalian Cells*, 5 SCI. TRANSLATIONAL MED. 1 (2013); Norman Moullan et al., *Tetracyclines Disturb Mitochondrial Function Across Eukaryotic Models: A Call for Action in Biomedical Research*, 10 CELL REPS. 1681 (2015).
[266] Meyer, *supra* note 160 at 3-4; Paraskevaidi, *supra* note 260, at 3-4.
[267] Meyer, *supra* note 160, at 3-4.
[268] Brunst, *supra* note 258, at 983.
[269] Meyer, supra note 160, at 9.
[270] *Id.* at 3-4; Paraskevaidi, *supra* note 260, at 2-4.

First, even if MRT could be safe and effective in principle (a hypothesis that is currently unsupported), exposure to mitochondrial disruptors during biogenesis and over the course of the child's life has the potential to undo theoretical mitochondrial correction as damage accumulates. Based on scientific concerns related to cross-talk between mtDNA and nDNA, this also raises questions of whether disrupting the naturally occurring cross-talk would have negative implications for the mitochondria's evolutionary ability to adapt to the influence of mitochondrial disruptors.[271] Finally, this area of research demonstrates that rare fatal disease arising from mitochondrial dysfunction merely constitutes the tip of the iceberg. Promoting MRT as a viable option distracts from the heavy burden of environmentally mediated mtDNA and nDNA damage quietly influencing the rates of common and chronic disease. Recognizing and reducing these exposure levels should constitute the focus of the inquiry, along with concurrent low risk interventions such as exercise and dietary measures, which have been shown to enhance mitochondrial function. [272]

2. Causes of Infertility

The FDA MRT Meeting also considered the possibility of clinical trials to explore using MRT to treat infertility, and some have suggested treating infertility constitutes the end goal.[273] Though the NAS Report limited its recommendation that the FDA limit applications to treatment of mtDNA disease, the FDA is not bound by NAS's recommendation. Furthermore, even if the

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[271] Stuart Newman, *CRISPR Will Never Be Good Enough to Improve People*, 30 GENE WATCH (2017) (discussing scientists' limited understanding of genetic mutations and the role of evolution to sustain an organism).
[272] Paraskevaidi, *supra* note 260, at 6. Paraskevaidi and colleagues suggest simple low risk measures such as exercise and nutrition carry the potential for positive impact because they encourage mitochondrial formation.
[273] Iishi, *supra* note 15, at 151; Don Wolf et al., *Mitochondrial Replacement Therapy in Reproductive Medicine*, 21 TRENDS IN MOLECULAR MEDICINE 68 (2015).

FDA were to approve an investigational new drug application related to MRT, the fertility clinic could subsequently use the approved MRT procedure off label for infertility and other purposes. Investigating the medical rationale of using MRT to treat infertility raises a similar set of findings with research demonstrating that rising rates of impaired fertility are likely due to a variety of complex environmental and lifestyle causes including aging, not inherent genetic flaws.[274]

A portion of infertility stems from aging, and as one gynecologist observed, trying to change biology is "incredibly difficult and expensive to alter."[275] Popular media articles and scholars have questioned the social messaging behind the cultural phenomenon of delaying motherhood, asking why addressing age related reproductive complications and limitations have become taboo.[276] During the FDA MRT Meeting, participants discussed a number of age related biological changes such as diminished ovarian function, risk of aneuploidy, genetic segregation errors, and oocyte structural defects.[277] If aging increases the risk of aneuploidy or mutations to

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[274] Theo Colburn et al., *Our Stolen Future* (1996); Ake Bergman et al. (eds.), *State of the Science on Endocrine Disrupting Chemicals*, WHO & UNITED NATIONS ENV'T PROGRAM (2012) [hereinafter "State of the Science"]; Carlos Guerro-Bosagna & Michael Skinner, *Environmentally Induced Epigenetic Transgenerational Inheritance of Male Infertility*, 26 CURRENT OPINION IN GENETICS AND DEV. 79 (2014); Evanthia Diamanti-Kandarakis et al., *Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement*, 30 ENDOCRINE REV. 293 (2009); *Fertility and Infertility and the Environment*, NAT'L CTR. FOR ENVTL. HEALTH, CTS. FOR DISEASE CONTROL & PREVENTION, https://ephtracking.cdc.gov/showRbFertilityInfertilityEnv.

[275] Viv Groskop, *The Fertility Industry is One That Sells Hope- Sometimes That Hope Is False*, THE GUARDIAN (June 1, 2015), https://www.theguardian.com/lifeandstyle/2015/jun/01/fertility-industry-sells-hope-false-delay-having-baby.

[276] *Id.*; *see* David Adamson, *The Hot Topic of Egg Freezing and What You Should Know*, THE HUFFINGTON POST (Sept. 2, 2016), http://www.huffingtonpost.com/dr-david-adamson/the-hot-topic-of-egg-freezing-and-what-you-should-know_b_11765436.html; Katie Hammond, *Egg Freezing: An Empowering Option for Women?*, RES. U. OF CAMBRIDGE (Nov. 17, 2014), http://www.cam.ac.U.K./research/discussion/egg-freezing-an-empowering-option-for-women.

[277] FDA Meeting, *supra* note 11, 75-77; 172-175.

nDNA contained in maternal oocytes, MRT would not address these concerns because the procedure transfers nDNA from the mother to the donor.[278]

In addition to age, research suggests lifestyle choices can directly impact both female and male fertility outcomes. Factors such as smoking, alcohol use, diet, and sedentary lifestyle have been shown to negatively correlate to fertility outcomes.[279] Some promising research suggests positive effects of dietary changes and moderate exercise as an avenue to improve fertility.[280]

Despite these potential causes, infertility is dramatically rising in the population of young adults in their twenties which has led researchers to investigate additional causes. Research implicates a variety of environmental toxicants including pesticides, PCBs, phthalates, parabens, and Bisphenol A that are present in our daily environment and act as endocrine disrupting chemicals (EDCs) contributing to rising rates of impaired fertility.[281] In 2012, the World Health Organization and the United Nations Environment Program published a report, "State of the Science on Endocrine Disrupting Chemicals" on the impact of EDCs on human reproduction.[282] Currently, there are eight hundred chemicals that are known or suspected to be capable of interfering with human reproduction.[283] Exposure to EDCs can interfere with hormone synthesis, conversion, and signaling, which can impair growth throughout the life cycle and

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[278] Kara Manke, *With Gene Disorders, The Mother's Age Matters, Not the Egg's*, NAT'L PUBLIC RADIO (July 7, 2014), http://www.npr.org/sections/health-shots/2014/07/07/328132687/with-gene-disorders-the-mothers-age-matters-not-the-eggs; Ross Rowsey et al., *Examining Variation in Recombination Levels in the Human Female: A Test of the Production-Line Hypothesis*, 95 AM. J. OF HUMAN GENETICS 108 (2014).
[279] Guerro-Bosagna & Skinner, *supra* note 274, at 80-83; *see also* Rakesh Sharma et al., *Lifestyle Factors and Reproductive Health: Taking Control of Your Fertility*, 11 REPROD. BIOLOGY & ENDOCRINOLOGY (2013).
[280] *Id.*
[281] *Id.*
[282] State of the Science, *supra* note 274.
[283] *Id.*, at vii.

reproductive capability.[284]

Scientists describe a period called the critical window of development during gestation and early infancy, during which exposure to toxicants can alter normal development and manifest in acute or long term health effects.[285] During fetal development, the brain and fetal tissue undergo rapid development along a specific pathway.[286] Any exposure to toxicants during this crucial stage could halt or alter the normal course of proper hormone signaling and fetal tissue differentiation leading to long lasting and permanent health deficits.[287] These deficits may manifest through a number of avenues in females including ovarian dysgenesis, premature ovarian failure, anovulation, and irreversible morphological abnormalities in the human reproductive tract.[288] Importantly, an extensive body of research demonstrates both females and males are affected by rising rates of infertility.[289] In males, the impact of EDCs may result in low testosterone, a decrease in semen quality, reduction in sperm, and deficiencies in sperm motility, disruption of testicular development, and abnormalities of the male reproductive tract.[290]

Exposures to EDCs during the critical window and throughout the course of one's life have the potential to exert epigenetic changes not only to the individual's somatic cells, but also to the germ cells.[291] This means EDCs are not only changing the individual's reproductive

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[284] *Id.*, at viii.
[285] *Id.*, at ix.
[286] *Id.*
[287] *Id.*
[288] Andre Marques-Pinto & Davide Carvalho, *Human Infertility: Are Endocrine Disruptors To Blame?* 2 ENDOCRINE CONNECTIONS R15 at 21 (2013).
[289] *Id.*
[290] Marques-Pinto & Carvalho, *supra* note 288, at 19; State of the Science, *supra* note 274, at 57-58, 65, 74; Guerro-Bosagna & Skinner, *supra* note 274, at 80-83.
[291] Guerro-Bosagna & Skinner, *supra* note 274, at 81-82.

capacities, but also transmitting altered epigenetic marks to subsequent generations and potentially compromising the offspring's fertility as well.[292]

As a whole, this research suggests that the medical rationale of using MRT to treat infertility contains numerous flaws. Even presuming MRT could ever be safe and effective, it fails to address impaired fertility that could be prevented through social policy movements that encourage reproduction during biologically viable years and lifestyle modifications that support fertility potential. MRT also would not address the various deficiencies in female reproductive capacity such as reproductive tract abnormalities or insufficient ovarian reserve. MRT would also not address any of the growing concerns related to male infertility. Scientific research in this area suggests a need to systematically address the underlying factors contributing to population level fertility impairment.

C. Assessing the Potential for Market Expansion

After deconstructing the medical rationale, proponents' claims that MRT could treat mitochondrial disease and infertility become less compelling. This raises questions of why proponents would aggressively push a highly risky experimental technology. Developing MRT to offer as the newest option in the treatment of infertility holds substantial value for industry revenue and commercial expansion, both domestically and as a means to increase the U.S. fertility industry's global market share.[293]

Statistics vary, but according to the Centers for Disease Control, approximately twelve percent of couples in the U.S. suffer from impaired fecundity, defined as the inability to get

[292] *Id.*, at 83-84.
[293] Claiborne et al., *supra* note 16, at 12.

pregnant or carry a baby to term.[294] The World Health Organization evaluated global rates of infertility, finding up to one quarter of couples of childbearing age suffer from infertility.[295] In the U.S., 62 million women of childbearing age are infertile and 7.4 million women seek fertility services during their life.[296] These figures translate into a lucrative industry and "sprawling commercial enterprise,"[297] estimated to be between $3 to 4 billion dollars in the United States, with demand growing approximately ten percent annually.[298]

Rising rates of impaired fertility combined with the promise of a genetically related child have produced a booming market. Having a genetically related child satisfies a deeply held primal desire, but as legal scholar Lisa Ikemoto observed, industry's focus on emotional stories "is compelling because it is real" but it "elides the commercial nature of the practice."[299] Focusing on the pathos of parental yearning distracts from the consumerism, including how potential parents also constitute vulnerable participants in their quest for parenthood.[300] Historian Nathaniel Comfort maintains prioritizing the technological imperative and mastery of science over nature categorizes emerging technology as a "humane" option for medical suffering

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[294] *Infertility*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/reproductivehealth/Infertility/.
[295] *Global Prevalence of Infertility, Infecundity, and Childlessness*, WHO, http://www.who.int/reproductivehealth/topics/infertility/burden/en/.
[296] Gregorio, *supra* note 226, at 1285.
[297] Ikemoto, *supra* note 226, at 278.
[298] *Fertility Market Overview*, HARRIS WILLIAMS & CO. (May 2015), http://www.harriswilliams.com/sites/default/files/content/fertility_industry_overview_-_2015.05.19_v10.pdf. Harris Williams estimates $1.7-2.5 billion is spent on ART services annually in the U.S., and approximately $1.5 million is spent on fertility medications in the US. It also estimates the global fertility market is between $30-40 billion annually. *See also* Michael Cook, *IVF World Market to Reach US $12Billion*, BIOEDGE (March 11, 2017), https://www.bioedge.org/bioethics/ivf-world-market-to-reach-us12-billion/12225.
[299] Ikemoto, *supra* note 226, at 306-07.
[300] Suter, *supra* note 251, at 237; Newman, *supra* note 271.

offered with a "veneer of benevolence."[301] Yet Comfort notes viewing new technology in this manner fails to situate it within the broader context of a free market system that brutally capitalizes on the newest technology, at times at the expense of those who seek it. [302]

We must be cautious of the commercial market driving the adoption of new technology such as MRT, because the market prioritizes expansion and profit increase as a primary goal, which creates a conflict of interest with parents, children, and egg donors in MRT.[303] Minimal regulation combined with a high demand for services means the ART industry has little incentive to collect and analyze important data related to risk, outcomes, and efficacy beyond basic statistics related to viable pregnancies.[304] This shifts external costs related to latent risks and long term harm onto parents, donors, and children.[305] Unlike other classes of physicians who are passive providers, the fertility industry constitutes influential stakeholders where the physicians themselves consistently push for implementing risky experimental techniques as a means of expanding and increasing their market position.[306] If the fertility industry offers MRT in the U.S. pursuant to an FDA submission, this provides the imprimatur of safety and efficacy, even though the procedure may indeed pose long term and latent risks to the child and the child's offspring. Alternatively, the fertility industry may opt to forgo pursuing an investigational new drug submission but continue to offer MRT as a service the clinic coordinates to perform in another country.

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[301] Comfort, *supra* note 168.
[302] *Id.*
[303] Frankel, *supra* note 201.
[304] Suter, *supra* note 251, at 256-57.
[305] *Id.*
[306] Ikemoto, *supra* note 226, at 280-281; Suter, *supra* note 251, at 255; Kimberly Mutcherson, *Welcome to the Wild West: Protecting Access to Cross Border Fertility Care in the United States*, 22 CORNELL J. L. & PUB. POL'Y 349, 390-91 (2012).

Permitting, or even insisting, that individuals have access to risky experimental reproductive techniques has the potential to increase reproductive tourism into the U.S. as destination point for MRT.[307] Legal scholars have described how the convergence of globalization and the fertility market has resulted in potential parents crossing borders, seeking a country that permits them to fulfill their parental desire.[308] Restrictions in some countries have led to strategic jurisdictional forum shopping, precisely illustrated by the example of Dr. Zhang. Potential parents willing to travel great lengths may seek out niche markets that offer what appear to be the newest and best products and services in an attempt to achieve a pregnancy, or even elect to use MRT as an energetic corrective preventive practice against aging, obesity, and common disease in the future child.[309]

VII. Recommendations

Promoting MRT as a method to assist suffering potential parents fails to acknowledge the substantial weight assigned to scientific innovation and commercial profit incentives driving the scientific and fertility industry. This framing not only lacks transparency, but appears ethically troublesome based on the concerted effort during the policymaking process to dismiss the risks involved in MRT and modifying the human germline.[310] As one bioethicist questioned, "Who is applying the brakes? Private entities are profit driven, which is the last question we should consider when altering the human race."[311] The U.S. appears poised to not only to accept

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[307] Mutcherson, *supra* note 306, at 371.
[308] *See generally* Mutcherson, *supra* note 306; Ikemoto, *supra* note 226; April Cherry, *The Rise of the Reproductive Brothel in the Global Economy: Some Thoughts on Reproductive Tourism, Autonomy, and Justice*, 17 U. PA. J. L. & SOC. CHANGE 257 (2014).
[309] During the FDA MRT Meeting, participants suggested using MRT as an option to not only "treat" mitochondrial disease and infertility, but some participants also suggested it could be a treatment for age, obesity, and common disease. *See* FDA Meeting, *supra* note 11, at 208.
[310] *Id.* at 182-183.
[311] Frankel, *supra* note 201.

inflated promises of MRT, but to do so through a policymaking process that provided the appearance of deliberation while issuing conclusions against the weight of the scientific evidence. This sets a dangerous precedent, where implicit prioritization of scientific exploration and commercial interests directs governance outcomes in a manner that implicitly subverts considering risks to human health. In this instance, the weight of the scientific evidence not only suggests creating children through MRT may not be safe or effective, but that the procedure may impose new health deficits such as an increased risk of developmental disorders, latent fatalities, expedited aging, cancer, and congenital abnormalities.

Although some appear resigned to the power of these "baby markets,"[312] I assert we have a duty to use federal regulation as a mechanism to insulate parents, donors, and children from substantial risks inherent in MRT as well as new technological iterations that promise to correct genomic flaws by prohibiting modification of the human germline. Commercial and scientific interests have painted a false double bind: regulation that entails callous prohibitions stifling innovation to that could otherwise help parents have healthy children, or an unhampered free market wherein the fertility industry can produce miracles. Confined to the impossible choices in this narrative blocks us from considering the crucial questions raised here: such as whether the scientific risks mirror the policymaking outcome; why the discussion glosses over risks to oocyte donors; how the science fails to support the medical rationale for MRT; and the inappropriateness of permitting commercial motivations to drive the adoption of MRT.

Rather than prioritizing scientific ingenuity and economic profit, the U.S. and other nations have a duty to enact measures that discourage risky experimentation on future generations through MRT and other forms of germline modifications. I affirm the proposition

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[312] *See generally* Suter, *supra* note 251.

that future generations have a right to an "untampered genome." [313] I further assert that each individual has a human right to be born without intentional germline interventions, and we have an ethical duty to investigate and mitigate sources that threaten the integrity of our health. This duty encompasses a diligence to properly situate and analyze whether proponents' medical rationale matches available evidence or constitutes a strategic appeal to our pathos. This stance against MRT and other germline interventions coincides with the scientific opinion that our inability to accurately predict the outcomes of potential interventions means germline modifications including MRT should not be permitted.[314] Germline interventions pose significant risk and carry the threat of unintended consequences that are both irreversible and permanent.[315] The consensus against germline modifications set forth by UNESCO's International Bioethics Committee, the Council of Europe, and numerous other nations should remain intact to protect the health of future generations.

New regulations enacted in other nations should affirm this prohibition through unambiguous legislative measures. At the federal level, nations should not rely on funding restrictions, but enact criminal prohibitions for human germline modification of human embryos. These statutes should prohibit the creation of embryos with germline modifications for implantation and include additional mechanisms to dissuade implantation. Nations should recognize the transnational nature of this research and the convergence of forum shopping and reproductive tourism. As a mechanism to deter avenues of legal circumvention through reproductive tourism, nations should include prohibitions on recruitment of potential patients for

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[313] *See Human Enhancement*, STAN. ENCYCLOPEDIA OF PHIL., https://plato.stanford.edu/entries/enhancement/.
[314] Newman, *supra* note 271; Lanphier, *supra* note 141.
[315] Comfort, *supra* note 168.

impermissible procedures to create embryos with germline modifications, whether through MRT or another procedure, performed in another nation. These laws could also include a prohibition on the import and export of unauthorized human embryos for implantation. The statute should specify explicit criminal penalties that would reflect the gravity for potential harm of experimenting on future generations.

VIII. Conclusion

UNESCO's International Bioethics Committee cautioned against a number of elements that appear to be driving the shift in U.S. policy to permit MRT. Proponents of MRT employed reductionist explanations and simplified mitochondria's function, belying its complex evolutionary role, its impact on nDNA expression, and dismissed extensive doubts in the scientific community pertaining to safety and efficacy. Media articles in the U.S. praised Dr. Zhang for traveling to Mexico to perform MRT as a "therapy" to "save lives" and circumvent FDA jurisdiction. These actions directly contravened the International Bioethics Committee's directives for the media to avoid sensationalist journalism and renounce regulatory circumvention. During FDA meetings to discuss MRT to treat mitochondrial disease or infertility, many participants concluded the evidence falls "far short" of showing MRT could be safe and effective and asserted MRT could induce new permanent and irreversible health deficits in the child, in addition to existing risks arising from ART. MRT would also require increasing the pool of oocyte donors, which imposes potentially serious health consequences such as OHSS, impaired fertility, and increased risk of cancer on a class of women in exchange for payment to satisfy the reproductive projects of third parties. These risks pose significant burdens on both future children and oocyte donors. Furthermore, analysis of the medical rationale reveals MRT would not address a substantial portion of conditions related to mitochondrial dysfunction and

the complex factors influencing rising rates of infertility. The NAS Report's conclusion that conducting clinical investigations for MRT is ethically permissible is unsupported by the weight of the evidence and appears to prioritize the technological imperative and its potential to grow the U.S. global market share in novel fertility industry options.