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 Therapy'

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[1] and 1 in 6,000.[2] The symptoms of these diseases range from mild to severe.[3] 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'.[4] The prevalence of inheritable mitochondrial disease in Singapore has not been studied.[5]

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

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[1] Gorman et al. 'Prevalence of Nuclear and Mitochondrial DNA Mutations Related to Adult Mitochondrial Disease', *Ann Neural* 77 (2015): 753-759.
[2] Laura Bainbridge, *Understanding and Coping With Mitochondrial Disease* (Hamilton Health Sciences, 2010), 1.
[3] 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).
[4] Ibid.
[5] 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-modification-mitochondrial-10152826, accessed

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.[6]

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

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

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

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'.[7]

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 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.[8]

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'.[9]

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[7] William May, *Catholic Bioethics and the Gift of Human Life* (Huntington, Indiana: Our Sunday Visitor, 2000), 53.
[8] Ronan O'Rahilly and Fabiola Müller, *Human Embryology & Teratology*. 3rd Edition. (New York: Wiley-Liss, 2001), 8.
[9] Ibid., 28.

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.[10]

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".[11]

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 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

[10] 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.
[11] Ibid.

> cases the production of the resulting 'combi-embyro' is totally depersonalising.[12]

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 entitled, '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).[13] 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'.[14]

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.[15]

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

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[12] 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.

[13] 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.

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

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

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 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.[16]

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'.[17]

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.[18] Borrowing from the language of the Nicene Creed, the Anglican theologian Oliver O'Donovan reminds us that children are 'begotten, not made'.[19] The shift from 'procreation' to 'reproduction' – from the metaphor associated with the mutual self-giving 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*.[20]

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

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[16] 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.
[17] César Palacious-González, 'Are There Moral Differences Between Maternal Spindle Transfer and Pronuclear Transfer?' Medicine, Health Care, and Philosophy 2017, 20(4), 10.
[18] Leon Kass, *Towards a More Natural Science* (New York: The Free Press, 1085), 48.
[19] Oliver O'Donovan, *Begotten or Made?* (Oxford: Oxford University Press, 1984).
[20] 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

> 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 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.[21]

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'.[22] 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'.[23] MGRT, which uses the healthy

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[21] 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.

[22] '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.

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

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.[24] 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.[25]

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.[26] When asked about their initial reaction to the procedure, 44% said they were 'very' or 'fairly' positive and only 15% were 'very' or 'fairly' negative.[27]

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

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[24] 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/.

[25] 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).

[26] 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.

[27] Ibid.

parents'.[28] 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'.[29] 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.[30]

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'.[31] 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'.[32] 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.[33]

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[28] 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.
[29] Ibid.
[30] 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.
[31] Fransçoise Baylis, 'Black as Me: Narrative Identity', Developing World Bioethics 3, 2003, 142.
[32] 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.
[33] 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.

'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'.[34]

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,[35] 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'.[36] 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'.[37]

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'.[38] The BAC paper has noted these international regulations on germline modification (pp. 14-15). In an article entitled, 'Which Ills to Bear', Alexander Capon

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[34] Ibid.
[35] Amy M. Lardy, 'Redefining Motherhood: Determining Legal Maternity in Gestational Surrogacy Arrangements', Drake Law Review, Volume 51, No. 3, 12003: 605-632.
[36] Amy Leiser, 'Parentage Disputes in the Age of Mitochondrial Replacement Therapy', 431, http://georgetownlawjournal.org/files/2016/01/Leiser-ParentageDisputesintheAgeofMitochondrialReplacementTherapy.pdf (accessed May 2016).
[37] Ibid.
[38] 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.

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.[39]

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 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.[40]

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.[41] 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.[42]

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

[40] *Instruction* Dignitas Personae *On Certain Bioethical Questions*, http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_20081208_dignitas-personae_en.html, accessed 24 April 2015.

[41] 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.

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

In response, the Council would like to point out that nomenclatures for emerging and new biotechnologies are sometimes coined in a notoriously haphazard fashion.[43] 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'.[44] 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.[45] Writing just before the UK decision to trial MGRT, Marcy Darnovsky, Executive Director of the 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.[46]

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

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MitochondrialTransplants-Vers01-6.pdf.

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

[44] 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.

[45] 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.

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

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'.[47] 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'.[48]

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.[49] Another study detects a possible connection between mtDNA variation and susceptibility to alcoholism.[50] 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.[51] 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'.[52] 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.

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[47] 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.

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

[49] 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.

[50] 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.

[51] 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.

[52] 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.[53] In addition, if SSAs are used even in debates on older issues in bioethics like physician-assisted suicides and euthanasia,[54] 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!).[55]

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

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[53] *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 **....")**.

[54] *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.

[55] 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.

without off- target mutations.

Furthermore, some people might use the state-of-the- art genetic engineering for enhancement.[56]

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 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'.[57] 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.[58] 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.[59] 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

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[56] Tesuya Ishii, 'Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification', *Reproductive Medicine Online* (2014) 29, 150-155.
[57] Human Assisted Reproductive Technology Act 2004, Section 4 a and b. http://www.legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319248.
[58] 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.
[59] K Reinhardt, D.K. Dowling, E.H. Morrow. 'Mitochondrial Replacement, Evolution, and the Clinic'. *Science* 2013; 341: 1345–6.

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'.[60] 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.[61] 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.[62] 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'.[63]

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.[64] 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 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.[65] 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,[66] cancer,[67] and congenital

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

[61] 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.

[62] 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.

[63] BAC Consultation Paper 2018.

[64] 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.

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

[66] 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,

abnormalities.[68] To add to these the possible risk of imprinting disorders and complications resulting from mtDNA-nDNA incompatibility brought about by MGRT is medically irresponsible[69] 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.[70]

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'.[71] 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.[72]

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

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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.

[67] 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, Schouten-van 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.;

[68] 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.

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

[70] 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.

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

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

population, and the alternatives available for women with mitochondrial disorders,[73] 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.[74]

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[73] 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.

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

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 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"'.[75]

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. 19). 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

[75] Ibid., 106.

> 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 …[76]

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'.[77] 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 and another receives it.[78] 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.[79] 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.[80] 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.[81]

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[76] Françoise Baylis, 'Ethical Objections to Mitochondrial Replacement', *Impact Ethics*, July 2, 2013.
[77] Quoted in G Vogel, 'FDA Considers Trials of Three-Parent Embryos', Science, 2014, 343: 827.
[78] James C. Petersen, Genetic Turning Points: The Ethics of Human Genetic Intervention (Grand Rapids, Michigan: Eerdmans, 2001), 311.
[79] Daniel Callahan, 'What Obligations Do We Have to Future Generations?' in *Responsibilities to Future Generations: Environmental Ethics*, ed. Ernest Patridge (Buffalo: Prometheus, 1981), 76.
[80] Donald MacKay, *Human Science and Human Dignity* (Downers Grove, Ill: Inter-Varsity Press, 1979).
[81] Thomas Sieger Derr, 'The Obligations to the Future', in *Responsibilities to Future Generations: Environmental Ethics*, ed. Ernest Patridge (Buffalo: Prometheus, 1981), 41-2.

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'.[82] 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'.[83] 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'.[84] 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.[85]

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'.[86] 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

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[82] 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.
[83] Frankel and Chapman, 4.
[84] Ibid., 10.
[85] 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 (*emphasis mine*).
[86] Alyssa Lane, et al, '"Mitochondrial Replacement" Technologies and Germline Nuclear Modification', Society of Obstetricians and Gynaecologists of Canada, 2016, 3.

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.[87]

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'.[88] In addition, Lupron™ (leuprolide acetate), a drug commonly prescribed to egg donors has a range of side effects.[89]

In a paper entitled, 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.[90] 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.[91] 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 out: 'To be sure, egg donation raises significant moral and social questions relating to

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[87] www.ourbodiesourselves.org.
[88] 'Epidemiology and Prevention of Ovarian Hyperstimulation Syndrome (OHSS): A Review', *Human Reproduction Update*, Volume 8, no. 6, 2002, 567.
[89] 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.
[90] 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.
[91] F. Baylis, 'Babies with some animal DNA in them: a Woman's Choice?' *Int. J. Feminist Approach Bioethics* (2009)2: 75-96.

the dignity and health of women, even if the donors come forward voluntarily to offer their services'.[92]

The Council has raised some of these objections to egg donation in its response to a BAC Consultation paper in 2008.[93] 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.[94] 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.[95]

> 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.[96]

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.[97]

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

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[92] 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.
[93] 'Response to the Bioethics Advisory Committee's Consultation Paper entitled Donation of Human Eggs for Research', 2008, http://www.bioethics-singapore.org/images/uploadfile/14457%20PMAnnex%20C%20-%20Written%20Responses.pdf, C29-32.
[94] 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.
[95] Response, C-31.
[96] Ibid.
[97] Ibid.

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.[98]

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.

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