



Australian Government

National Health and Medical Research Council

Senate Community Affairs References Committee Inquiry into Mitochondrial Donation

NHMRC Submission

Introduction

The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research, for developing health advice for the Australian community, health professionals and governments, and for providing advice on ethical behaviour in health care and in the conduct of health and medical research.

NHMRC aims to achieve improved health and medical knowledge, including through funding research, translating research findings into evidence-based clinical practice, administering legislation governing research, issuing guidelines and advice for ethics in health and the promotion of public health. These functions reflect the role for NHMRC set out in its enabling legislation.

As required by the *National Health and Medical Research Council Act 1992*, the Australian Health Ethics Committee (AHEC, a Principal Committee of NHMRC) provides advice on ethical issues relating to health, and develops human research guidelines that are issued by the CEO of NHMRC. The *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research (ART Guidelines)*^a and the *National Statement on Ethical Conduct in Human Research*^b are relevant to this submission.

Through the Embryo Research Licensing Committee (ERLC) (a Principal Committee of NHMRC established under the *Research Involving Human Embryos Act 2002 (RIHE Act)*^c), NHMRC is responsible for administering the *Prohibition of Human Cloning for Reproduction Act 2002 (PHCR Act)*^d and the RIHE Act. These Acts regulate activities that would relate to mitochondrial donation and would have to be amended if mitochondrial donation were to be permitted in Australia.

There is no Commonwealth legislation that directly regulates the clinical practice of assisted reproductive technology (ART) in Australia. The RIHE Act (section 8 and section 11) requires all ART clinics to be accredited by the Reproductive Technology Accreditation Committee^e (RTAC) of the Fertility Society of Australia, which in turn requires clinics to comply with the RTAC Code of Practice in order to achieve accreditation. RTAC conducts its own reviews and audits to assess compliance. Victoria, New South Wales, South Australia and Western Australia have state legislation that regulates the conduct of ART in those states, but the other states and territories rely on the operation of the RTAC Code of Practice. The RTAC Code of Practice requires clinics to comply with the ART Guidelines.

^a <https://www.nhmrc.gov.au/guidelines-publications/e79>

^b <https://www.nhmrc.gov.au/guidelines-publications/e72>

^c <https://www.legislation.gov.au/Details/C2016C00968>

^d <https://www.legislation.gov.au/Details/C2017C00306>

^e <https://www.fertilitysociety.com.au/rtac/>

(a) the science of mitochondrial donation and its ability to prevent transmission of mitochondrial disease

Mitochondria – functions and role in disease

Mitochondria are small structures found in cells of the body that provide energy for cells to function. They have a small amount of DNA – 37 genes compared to approximately 20,000 – 30,000 genes in nuclear DNA. More than 1000 nuclear genes relate to mitochondrial functions.¹ Unlike nuclear DNA which is inherited from both parents, mitochondrial DNA (mtDNA) is only inherited through the maternal line. Another difference between nuclear DNA and mtDNA is the number of copies of each type of DNA that can be found in each cell. There are two copies of each of 23 chromosomes in the nuclear DNA of each somatic cell (see Glossary). In contrast, there are varying numbers of mitochondria in different cell types and varying numbers of copies of mtDNA in each mitochondrion. For example, some cells may have 100 copies of mtDNA while human eggs have up to 500,000 copies.¹

Mitochondrial disease can be caused by mutations in nuclear DNA or mitochondrial DNA (mtDNA – see Glossary) and affects the way mitochondria function. Due to the mitochondria's role in energy production, mitochondrial disease particularly affects the organ systems that use the most energy. The symptoms of and prognosis for mitochondrial disease depend on the type and number of mutations and how the affected mitochondria are distributed among the tissues and organs. Mitochondrial disease can significantly affect the health and life expectancy of the individual and can be fatal. The most common presenting symptom is fatigue. Some signs and symptoms tend to occur together and subgroups of symptoms have been identified such as:

- mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- myoclonic epilepsy with ragged-red fibres (MERRF)
- Leigh syndrome.²

Given the variability in how mitochondrial disease may present, diagnosis can be difficult. Currently it may be possible to prevent the transmission of some forms of mitochondrial disease using preimplantation genetic diagnosis (PGD, see Glossary). However, PGD is not effective for detecting all types of mitochondrial disease.

If the mutation affects a nuclear gene, then ART combined with PGD may allow a woman with mitochondrial disease to have her own biological child who does not carry the disease. If the mutation affects a mitochondrial gene, but the woman with mitochondrial disease happens to have mitochondria with different versions of the affected gene^f, then ART with PGD may again allow selection of unaffected embryos so she can have her own biological child. However, if the mutation affects all her mitochondria then PGD is not useful as all her embryos will carry the mutation leading to mitochondrial disease in the child.

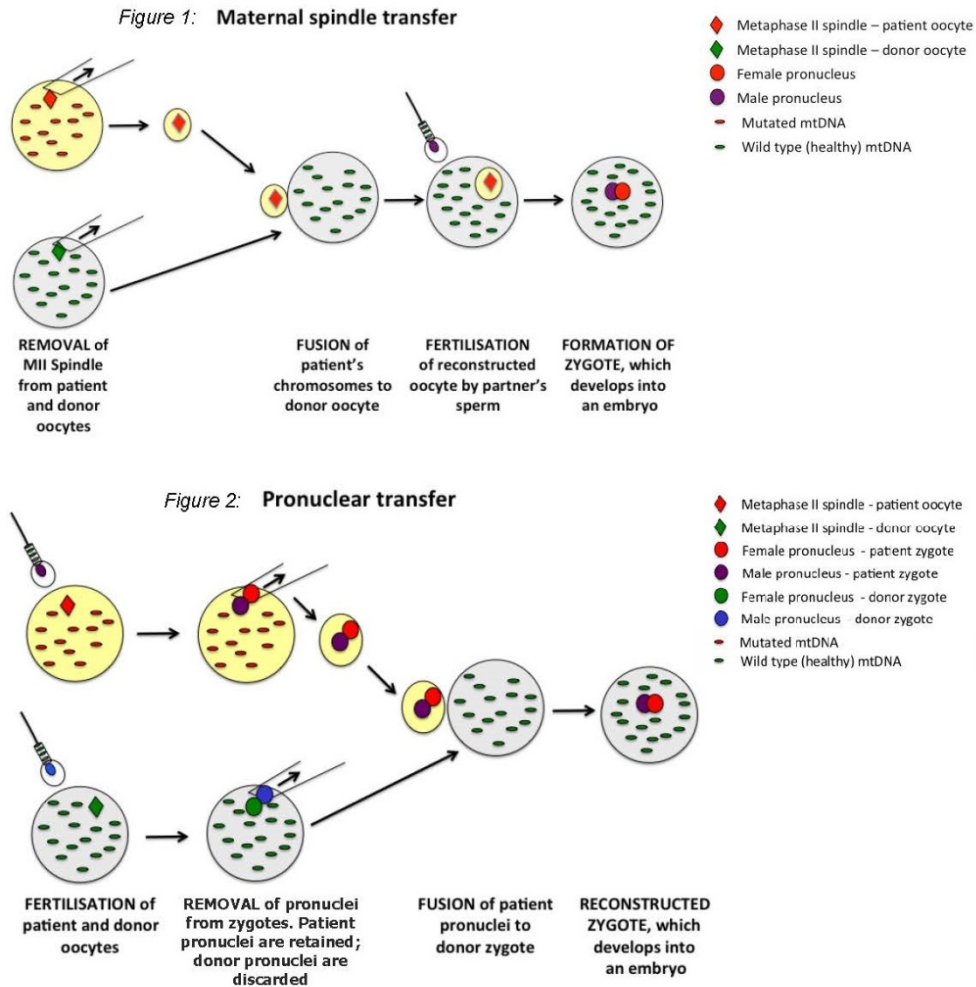
Mitochondrial donation

Techniques aiming to prevent the transmission of mitochondrial disease from a woman to her children are directed towards overcoming this third situation and towards women in the second category whose mitochondria have high levels of disease-causing mutations. These techniques are known as mitochondrial donation, mitochondrial replacement or mitochondrial transfer (see Glossary).

The goal of mitochondrial donation is to create an embryo with nuclear DNA from both parents and mitochondria (including mtDNA) from an egg donor without mitochondrial disease. There are several methods for doing this, all of which require women who do not have mitochondrial disease to donate eggs to the couples who are trying to have a baby which is the biological child of both parents.

^f This is known as heteroplasmy. The proportion of affected to unaffected mitochondria will affect the severity of mitochondrial disease. The higher the levels of affected mitochondria the more likely the person is to suffer severe disease. In addition, higher levels of affected mitochondria will reduce the likelihood that an unaffected or minimally affected embryo can be created using ART. The situation where all copies of mitochondrial DNA are identical is known as homoplasmy.

Current research is concentrating on two methods, maternal spindle transfer (MST) and pronuclear transfer (PNT), which are illustrated in Figures 1 and 2 (see Glossary). Other methods for achieving the same outcome have been explored and new ones may be developed in the future.



Figures reproduced with permission of Justin C. St John

Figures 1 and 2: Diagrams showing the process of maternal spindle transfer (MST) and pronuclear transfer (PNT).

In MST, a donated egg is modified by replacing the donor's nuclear DNA with the nuclear DNA from the mother. The reconstructed egg, which includes the mother's nuclear DNA and the egg donor's mitochondria, is fertilised with sperm from the father. In PNT, eggs from the mother and egg donor are fertilised with the father's sperm creating two zygotes: a mother/father zygote and a donor/father zygote (see Glossary). The nuclear DNA from the donor/father zygote is then removed and replaced by the nuclear DNA from the mother/father zygote.

In both techniques, the reconstructed embryos contain DNA from three people: nuclear DNA from the mother and father and mtDNA from the egg donor. If the reconstructed embryo is female and the resulting girl reaches adulthood and has her own children they will receive the egg donor's mtDNA. That is, the process of mitochondrial donation makes changes to the girl's genome which will be inherited by future generations.

It should be noted that the techniques do not completely eliminate the mother's mtDNA. Using current techniques, some of her mitochondria will be transferred with the nuclear DNA, although the amount of carryover can be minimised by expert practitioners.^{1,3,4} Some research indicates that levels of the mother's mtDNA may vary between different tissues in the resulting child⁵ and may increase after birth.^{3,4} This may mean that the child could develop mitochondrial disease at some stage.

(b) the safety and efficacy of these techniques, as well as ethical considerations

In September 2016, it was reported that a baby boy had been born following the use of MST to prevent the transmission of Leigh syndrome (a form of mitochondrial disease). This is the first reported birth using this technique.⁹ The embryo had been created by Dr John Zhang in a clinic in New York and had been transported to a clinic in Mexico for transfer to the mother^{h,5}. The baby was reported to be healthy at the age of seven months, but varying levels of his mother's mtDNA were detected in different tissues immediately after his birth. Although he will receive regular physical and neurological checks, his parents have requested no more testing for mtDNA unless there is a clinical benefit. Consequently, it may be difficult to assess the long-term success of the procedure.

Given its experimental nature, if the safety and efficacy of mitochondrial donation are to be adequately assessed, the ongoing monitoring and assessment of the medical and social consequences for families using it are essential to ensure evidence-based clinical practice and policy-making.^{1,4} Ideally, this monitoring would be multi-generational, that is, children born following mitochondrial donation would be monitored into adulthood and their children, if any, would also be monitored. However, while the parents may have consented to ongoing monitoring on behalf of the child, the child has not been involved in this decision and may not consent to long-term follow-up. Therefore, while the importance of follow-up for the safety and well-being of the child can be emphasised, there are significant ethical issues associated with ongoing monitoring that would need to be explored further.

There are likely to be a range of opinions and perspectives within the community about the ethics of mitochondrial donation. More information about the process for developing an ethical framework is included at (e) below.

Mitochondrial donation depends on the availability of donated eggs from women unaffected by mitochondrial disease. Therefore the needs and concerns of women who are potential egg donors must be recognised in public discussion of mitochondrial donation. As with the donation of eggs to women for use in ART, trade in eggs, informed consent and coercion to donate may be issues of concern. However, the egg donor's genetic connection to a child born after mitochondrial donation differs from the situation in ART. Chapters four and five of the ART Guidelines provide guidance but do not directly address issues in mitochondrial donation.

(c) the status of these techniques elsewhere in the world and their relevance to Australian families

United Kingdom (UK)

In February 2015, the UK became the first country in the world to allow the use of mitochondrial donation, with regulations coming into force in October 2015. This came at the end of a long policy making process, including four reviews of the science,^{4,6-8} a public consultation on the social and ethical issues⁹ and an ethical review conducted by the Nuffield Council on Bioethics.¹⁰ The fourth scientific review concluded that "it is appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients."⁴ On 15 December 2016, following publication of the fourth scientific review,⁴ the Human Fertilisation and Embryology Authority (HFEA, see Glossary) announced that specialist clinics in the UK could apply for a licence to use mitochondrial donation to treat severe mitochondrial disease.¹¹ The HFEA established a detailed Code of Practice for use of mitochondrial donation¹² and a HFEA committee approves access to treatment on a case-by-case basis. The Code of Practice covers aspects such as:

- the consent process
- the information required to be provided to the participants

⁹ Subsequently, there were media reports of two births following the use of mitochondrial donation to overcome age-related infertility.

^h Five embryos were created, but only one developed to the stage where it could be transferred to the mother.

- selection criteria for gamete (egg and sperm) providers
- the requirement for a clinic to hold a licence authorising it to offer mitochondrial donation at a designated site
- the requirement for HFEA to approve individual patients' access to mitochondrial donation and for those patients to be at high risk of transmitting mutations that will lead to serious mitochondrial disease
- the requirement that only named embryologists are permitted to undertake the procedure
- the expertise available in the clinic including mitochondrial disease specialists, reproductive specialists, embryologists, clinical geneticists, genetic counsellors and molecular geneticists
- the requirement for a documented process for long-term medical follow-up of children born following mitochondrial donation, provided patients have consented to that follow-up
- the requirement to report to the HFEA if the clinic becomes aware of any adverse outcomes following treatment involving mitochondrial donation.

The first and only treatment licence to date was issued to Newcastle Fertility at Life on 16 March 2017.¹³ One embryologist is authorised to manipulate eggs and embryos in order to create embryos with healthy mitochondria. In February 2018, the HFEA announced that two women had been approved to receive this treatment.¹⁴

United States of America (USA)

In the USA, the Food and Drug Administration (FDA) commissioned a report published by the National Academies of Sciences, Engineering and Medicine on mitochondrial donation, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations*, which was released in February 2016 (NASEM report)¹ and the recommendations summarised.¹⁵ The report stated that mitochondrial donation is ethically permissible but that initially only male embryos¹ should be transferred. The reason given for this decision was 'the need to proceed slowly and to prevent potential adverse and uncertain consequences of [mitochondrial replacement techniques] MRT from being passed on to future generations'. Allowing female children to be born would be contingent on adequate follow-up of male children and satisfactory findings on the intergenerational effects from animal studies. It appears that Congressional approval would be required for the decision to be implemented and this was reported as being unlikely at that time.

In support of its conclusion, the NASEM report also recommended:

- Clinical investigations be limited to women who otherwise would be at risk of transmitting serious mitochondrial disease such that the clinical presentation of the disease is predicted to lead to early mortality or substantial impairment of basic function.
- If the intended mother at risk of transmitting mitochondrial disease will also carry the pregnancy, professional opinion should be sought as to whether she is capable of completing the pregnancy without risk of serious adverse outcomes to her health or the health of the fetus.
- The health and well-being of any children born as a result of the use of mitochondrial donation should have priority when balancing the risks and benefits of the design of investigations, eligibility of prospective mothers, numbers of participants and timing of investigations.
- Clinical investigation protocols should be designed and standardised to the extent possible so as to minimise the number of variables and enable valid comparisons and pooling of outcomes across groups, including internationally.
- Clinical investigations should collect long-term information about psychological and social effects on children born.

Consent processes for intended parents should reflect the importance of long-term follow-up and how this would be part of the experience of any child born. This would include parental consent and then the child's

ⁱ It should be noted that the requirement to transfer only male embryos would require that all embryos were subjected to embryo biopsy and preimplantation genetic diagnosis prior to transfer of the selected embryo to the mother. This contrasts with the UK prohibition on biopsy of embryos which have undergone mitochondrial donation.

own assent and eventual consent to monitoring and research procedures performed from birth, up to and possibly beyond the child's reaching adulthood.

Following the reports of the birth of the child following the use of MST (see above) the FDA directed Dr Zhang to cease his activities in relation to mitochondrial replacement techniques as the activities did not and could not comply with the FDA's regulations. It appears that Dr Zhang used the MST procedure without the necessary approvals from the FDA and that Congress has prohibited the FDA from accepting applications for clinical investigations that "involve a human embryo ... intentionally created or modified to include a heritable genetic modification" so it is not possible to obtain approval.¹⁶

Canada

The use of mitochondrial replacement technologies is prohibited in Canada as there is a prohibition on altering the genome of an in vitro embryo in a way that is capable of being transmitted to descendants.¹⁷

(d) the current impact of mitochondrial disease on Australian families and the healthcare sector

As collection of data on this issue is outside NHMRC's remit, NHMRC does not have any authoritative information.

(e) consideration of changes to legal and ethical frameworks that would be required if mitochondrial donation was to be introduced in Australia

Comments on this term of reference are provided under the following headings:

- considerations related to establishing the capacity for mitochondrial donation in Australia - research, training, establishing centre(s) of excellence
- current legislative situation (research and reproduction)
- comparison with the UK regulatory model
- ethical frameworks.

Establishing the capacity for mitochondrial donation in Australia

As noted at (c) above, the UK has issued one licence permitting mitochondrial donation. The Code of Practice is very detailed and covers all aspects of how the procedure is to be conducted. The requirement that the procedure can only occur at the licensed site and be conducted by licensed personnel highlights the technical complexity of the procedure and the significant consequences of 'getting it wrong'.

The team at Newcastle Fertility at Life, UK, has been conducting research under licence and building its expertise in mitochondrial donation since 2005.¹⁸ This research has included the creation and then destruction of many hundreds of human embryos under licence as the methods were developed and refined.^{3,1} Human eggs were obtained in two ways. ART patients at the Newcastle clinic can donate some of their eggs to the research project and receive a discount on their treatment costs. Women who are not undergoing ART treatment can also donate eggs to the research. These women receive £500 per donation cycle. Payment for eggs is prohibited in Australia (see below).

The UK regulatory approach suggests that allowing one or a small number of centres in Australia to establish the capability and to conduct research, validation and training activities, which include the creation and destruction of human embryos, is a necessary preliminary step before mitochondrial donation is conducted clinically in Australia. The alternative – allowing clinical use, but prohibiting the creation of embryos for research, training and validation – means that any children born following the first use of mitochondrial donation in Australia would bear the increased risk associated with establishing expertise in the new technique.

In addition, UK patients are strongly encouraged to consent to follow-up monitoring of their children. If mitochondrial donation is permitted in Australia, a similar protocol, conducted within a 'research context' or a clinical trial, is recommended to increase the evidence base for the safety and efficacy of this technique.

ⁱ The studies described in reference 3 reported the use of 523 human eggs to create zygotes that were used for PNT studies. These experiments were some of many conducted by the group at Newcastle Fertility at Life.

Current legislative situation – Research and Reproduction

Research: In Australia, ERLC administers the licensing framework, which regulates research and some training activities that involve the use of human embryos. Under the PHCR Act and the RIHE Act, some research into PNT would be permissible under licence, but research into MST would not be permitted. This is due to how the legislation applies in the context of the different ways that embryos are created using each technique. However, the end result of both techniques is the same – an embryo which contains DNA from three people.

In PNT, two zygotes are created, but the removal of the nuclear DNA destroys them before the first cell (mitotic) division when the zygote becomes a two-celled embryo. Paragraph 20(1)(e) of the RIHE Act would allow a licence to be issued for this step. The creation of the reconstructed embryo could also be licensed under paragraph 20(1)(c) and it could be maintained in culture to assess the success of the procedure provided it was discarded before 14 days had elapsed (PHCR Act section 14). Consequently, research to refine the technique of PNT could be conducted under licence in Australia. While not without some doubt, the same legislative provisions may allow a clinic to apply for a licence to conduct training and validate the technique, although there would be little benefit in doing this if mitochondrial donation for reproduction was prohibited.

Australian legislation is silent on the construction of an egg with mtDNA from the donor and nuclear DNA from the mother in MST. However, the final step involves using fertilisation to create an embryo that contains genetic material provided by more than two people. That step is prohibited by section 13 of the PHCR Act and therefore research into MST could not be conducted in Australia.

In other words, the two methods have the same aim, and lead to the same outcome, but under Australian law research into one technique is prohibited and the other is allowed.^k This highlights the difficulty of prohibiting particular techniques in legislation, given evolving research which may offer several routes to achieve the same end result. If the legislation were to be amended, consideration should be given to regulating outcomes rather than techniques.

Reproduction: Mitochondrial donation for reproductive purposes is prohibited in Australia. Sections 13, 15 and 20 of the PHCR Act are particularly relevant. Under the Act, both MST and PNT lead to the creation of ‘prohibited embryos’ because the resultant embryos contain genetic material provided by more than two people (section 20 makes it an offence to implant a prohibited embryo in a woman). The use of MST is additionally prohibited by section 13 which prohibits creating an embryo by fertilisation if the embryo contains genetic material from more than two people.

Any legislative amendments to allow mitochondrial donation would need also to consider the potential to use the technique for purposes other than preventing the transmission of mitochondrial disease and whether those other purposes would be acceptable to the community. For example, it has been reported that mitochondrial donation was used in the Ukraine to improve the success rates of ART in older women by ‘rejuvenating’ their eggs with mitochondria from younger women.¹⁹ If the legislation were to be amended to allow mitochondrial donation, it would be necessary to consider whether this was to be permitted only to prevent severe mitochondrial disease or if other uses were acceptable.

The legislation could potentially be amended so that mtDNA was not included when determining how many people had contributed genetic material to an embryo (PHCR Act section 13, section 20). However, it would require careful drafting to ensure that this did not inadvertently allow other activities that may be unacceptable to the community.^l

^k It seems desirable that entities created by similar techniques should be treated equally under the legislation. NHMRC raised this issue in its submission to the Heerey Committee’s review of the legislation in 2011²⁰. However the Committee did not comment on this point as it did not consider the techniques were sufficiently advanced to be permitted under the legislation. Recommendation 7 stated “there should be no change to the current legislation in relation to the use of DNA from more than two persons”.

^l In this context, it should be noted that there are other technologies currently prohibited in Australia by the same sections of the PHCR Act that are the subject of active research overseas; for example, editing the human embryonic genome to modify particular genes to prevent the transmission of various genetic diseases. Furthermore, PNT has many similarities to somatic cell nuclear transfer which, depending on the context, may be used for therapeutic cloning (creation of an embryonic stem cell line

In addition, section 15 of the PHCR Act prohibits making heritable alterations to the human genome. If mitochondrial donation is to be allowed for reproductive purposes, this section would need to be amended as female children resulting from embryos created using mitochondrial donation have 'heritable alterations' to their genomes and will pass the alterations onto any offspring.^m However, it should be noted that there is considerable research overseas into editing specific genes in the nuclear DNA of human embryos.ⁿ If the legislation were to be amended to permit mitochondrial donation, any amendments to section 15 would need to be made in a way that takes into account the difference between altering mtDNA and editing the embryonic nuclear genome. Section 20 would then need to be amended to make it consistent with the rest of the amendments.

As noted above, mitochondrial donation relies on women who are unaffected by mitochondrial disease consenting to donate their eggs. To quote the most recent review of the PHCR and RIHE Acts (2011): "the process for a woman donating her eggs is intrusive and not particularly pleasant. It involves medication that has a hormonal affect over about ten days and hospitalisation for about half a day."²⁰ In Australia it is an offence carrying a 15 year term of imprisonment to give or receive, or to offer to give or receive, valuable consideration for eggs, embryos or sperm (PHCR Act section 21). Valuable consideration includes any inducement, discount or priority service in addition to payment. However, reimbursement for reasonable expenses is permitted.

Comparison with UK regulatory model

As noted in the Introduction, the Commonwealth does not regulate ART. In their current form, the PHCR and RIHE Acts do not extend to regulating the clinical use of mitochondrial donation and this may increase the complexity of any legislative amendments. This situation contrasts with the UK model where the HFEA regulates clinical ART and related research under one regulatory framework.

Ethical framework

Some within the community may object to any manipulation of human embryos that will be used for reproduction. Others may agree with the concept of mitochondrial donation to treat mitochondrial disease but may object to the idea that embryos could be created for research or training purposes and then discarded.

As noted in the Introduction, AHEC provides ethical advice and develops ethical guidelines for human research. Ethical guidance for activities currently permitted by the PHCR and RIHE Acts is provided in Part C of the ART guidelines. If mitochondrial donation were permitted in Australia, AHEC would need to develop the ethical framework through the process established by the NHMRC Act. This framework could be modelled on and possibly incorporated into the ART Guidelines, but preliminary consideration by a subgroup of AHEC and ERLC of the impact of emerging technologies including mitochondrial donation indicates that the ART Guidelines could not be applied unchanged to mitochondrial donation.

(f) the value and impact of introducing mitochondrial donation in Australia

The Australian Mitochondrial Disease Foundation reports that 1 in 5000 babies is born with severe mitochondrial disease and that approximately 1 in 200 people carries mtDNA mutations that could cause disease.²¹ NHMRC has been advised that, although the stated prevalence implies that approximately 4800 people in Australia have severe mitochondrial disease, their median lifespans are less than half that of the general population. Consequently the actual number may be closer to 2000.^o

matched to a particular individual, permitted under licence by PHCR Act section 22) or reproductive cloning which is prohibited by PHCR Act section 9. Monitoring whether PNT or SCNT had been carried out may not be straightforward.

^m Male children resulting from embryos created using mitochondrial donation carry the same alterations but cannot pass them to their descendants since mtDNA is only inherited from a person's mother.

ⁿ Researchers are editing the embryonic genome for various reasons but correcting mutations that lead to disease or disability is a major focus of the research. For some researchers, the goal is to refine the techniques to the point where they can be used on embryos that will be used for pregnancy. There may be calls to allow this in Australia.

^o Information provided by Professor David Thorburn PhD FHGSA FFSc(RCPA) Head, Mitochondrial Research, Murdoch Children's Research Institute. Honorary Professorial Fellow, Department of Paediatrics, The University of Melbourne

It must be emphasised that mitochondrial donation does not cure existing disease. If permitted in Australia, it may assist women with mitochondrial disease to have their own biological children while preventing the transmission of mitochondrial disease to future generations.

In light of the experimental nature of the technique and the size of the Australian population, should this technique be pursued in Australia, it may be appropriate to implement a regulatory framework that establishes a single Centre of Excellence to provide research and treatment in the context of long-term monitoring of any children born following mitochondrial donation, perhaps structured as a national clinical trial.

Conclusion

In summary, mitochondrial donation may allow women with mitochondrial disease caused by mutations in their mtDNA to have their own biological children with a reduced risk of transmitting mitochondrial disease to the children. However, mitochondrial donation does not treat existing disease and requires women who do not have mitochondrial disease to donate their eggs.

The research underpinning mitochondrial donation is still relatively new. The clinical use of mitochondrial donation has been legalised in one country, the UK, where one clinic and one scientist are authorised to provide the procedure. Only one child has been reported to have been born world-wide following the use of mitochondrial donation to prevent mitochondrial disease and it appears unlikely that information about the outcomes will be published. The circumstances leading to that birth did not comply with regulatory requirements in the USA.

If mitochondrial donation is to be permitted in Australia:

- The PHCR and RIHE Acts would need significant revision and amendment especially in relation to the offence provisions. If the legislation were to be amended, consideration could be given to regulating outcomes rather than techniques.
- Any proposal to amend the legislation would need to be supported by extensive public education and consultation on the complex scientific, ethical and social issues.
- It may be challenging to develop a suitable regulatory framework given the different regulatory pathways for embryo research and ART currently operating in Australia.
- The regulatory framework should allow research and address the need for training in and validation of the process before it is used for clinical treatment. This is likely to require the use of embryos in the research, training and validation activities.
- Consideration should be given to establishing the procedure in the context of a clinical trial to ensure evidence-based clinical practice and policy-making.

References

1. National Academies of Sciences, Engineering and Medicine, 2016. *Mitochondrial replacement techniques: ethical, social, and policy considerations*. Washington, DC: The National Academies Press, 3 February 2016. Online. Available: <http://www.nationalacademies.org/hmd/Reports/2016/Mitochondrial-Replacement-Techniques.aspx>. Accessed 8 February 2016.
2. Australian Mitochondrial Disease Foundation, "Mitochondrial Disease Information". Online. Available: <http://www.amdf.org.au/mito-info/>. Accessed 14 April 2016.
3. L. A. Hyslop *et al.*, "Towards clinical application of pronuclear transfer to prevent mitochondrial disease," *Nature*, vol. 534, pp. 383–386, 2016.
4. Human Fertilisation and Embryology Authority, "Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update". Online. Available: <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/10557.html>. Accessed 8 November 2017.
5. J. Zhang *et al.*, "Live birth derived from oocyte spindle transfer to prevent mitochondrial disease," *Reproductive BioMedicine Online* vol. 34, pp. 361-368, 2017. Online. Available: [http://www.rbmojournal.com/article/S1472-6483\(17\)30041-X/fulltext](http://www.rbmojournal.com/article/S1472-6483(17)30041-X/fulltext). Accessed 4 April 2017.
6. Human Fertilisation and Embryology Authority, "Review of scientific methods to avoid mitochondrial disease 2011". Online. Available: <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/6372.html>. Accessed 8 November 2017.
7. Human Fertilisation and Embryology Authority, "Review of scientific methods to avoid mitochondrial disease 2013". Online. Available: <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/8806.html>. Accessed 8 November 2017.
8. Human Fertilisation and Embryology Authority, "Review of scientific methods to avoid mitochondrial disease 2014". Online. Available: <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/8807.html>. Accessed 8 November 2017.
9. Human Fertilisation and Embryology Authority, "Mitochondria public consultation 2012". Online. Available: <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/9359.html>. Accessed 8 November 2017.
10. Nuffield Council on Bioethics, "Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review". Online. Available: <http://nuffieldbioethics.org/project/mitochondrial-dna-disorders/>. Accessed 24 May 2016.
11. Human Fertilisation and Embryology Authority, "HFEA permits cautious use of mitochondrial donation in treatment, following advice from scientific experts" 15 December 2016. Online. Available: <https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-permits-cautious-use-of-mitochondrial-donation-in-treatment-following-advice-from-scientific-experts/>. Accessed 8 November 2017.
12. Human Fertilisation and Embryology Authority, "Mitochondrial donation". Online. Available: <https://www.hfea.gov.uk/code-of-practice/33>. Accessed 8 November 2017.
13. Human Fertilisation and Embryology Authority, "HFEA statement on mitochondrial donation" 16 March 2017. Online. Available: <https://www.hfea.gov.uk/about-us/news-and-press-releases/2017-news-and-press-releases/hfea-statement-on-mitochondrial-donation/>. Accessed 8 November 2017.
14. BBC, "Doctors given approval for UK's first 'three-person' babies" 2 February 2018. Online. Available: <http://www.bbc.com/news/health-42918341>. Accessed 6 February 2018.
15. Z. Brennan, Regulatory Affairs Professionals Society, "Expert Committee: FDA should allow mitochondrial replacement trials under certain condition" 3 February 2016. Online. Available: <http://raps.org/Regulatory->

[Focus/News/2016/02/03/24245/Expert-Committee-FDA-Should-Allow-Mitochondrial-Replacement-Trials-Under-Certain-Conditions/](#). Accessed 2 May 2016.

16. Letter is linked from G. Everett, BioNews, "FDA reprimands US doctor trying to commercialise MRT" 14 August 2017. Online. Available: https://www.bionews.org.uk/page_96133. Accessed 15 August 2017.
17. Assisted Human Reproduction – Legislation and Guidelines: Prohibitions related to scientific research and clinical applications. Online. Available: <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/legislation-guidelines/assisted-human-reproduction/prohibitions-scientific-research-clinical-applications.html>. Accessed 4 April 2018.
18. Newcastle Fertility Centre at Life, "Inspection Report and Minutes 26 June 2006." Online. Available: <https://www.hfea.gov.uk/choose-a-clinic/clinic-search/results/17/>. Accessed 3 May 2018.
19. A. Coghlan, "Exclusive: '3-parent' baby method already used for infertility," *New Scientist*, 10 October 2016. Online. Available: <https://www.newscientist.com/article/2108549-exclusive-3-parent-baby-method-already-used-for-infertility/>. Accessed 18 October 2016.
20. National Health and Medical Research Council, Legislation Review Committee. "Legislation Review: *Prohibition of Human Cloning Act 2002* and *Research Involving Human Embryos Act 2002*," Reports, Canberra, June 2011. Online. Available: <http://www.nhmrc.gov.au/guidelines-publications/hc38/>.
21. Australian Mitochondrial Disease Foundation, Position Statement. "Mitochondrial replacement IVF techniques: maternal spindle transfer and pronuclear transfer" June 2014. Online. Available: <http://www.amdf.org.au/wp-content/uploads/2014/06/AMDF-position-statement-mtDNA-replacement-June-2014.pdf>. Accessed 5 May 2016.

Glossary

Key term	Description
AHEC	Australian Health Ethics Committee, a Principal Committee of NHMRC
ART Guidelines	The <i>Ethical guidelines on the use of assisted reproductive technology in clinical practice and research</i> issued by the CEO of NHMRC. The current version was issued in 2017.
Assisted reproductive technology (ART)	The application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction.
Embryo biopsy	A technique that involves removing one or more cells of an embryo. Embryo biopsy is usually done at either the cleavage stage (day two to three, eight-cell stage) or, more commonly, at the early blastocyst stage (day five, 150 cells). The cells that are removed can then be tested for a specific genetic mutation that leads to genetic disease or for overall chromosome normality.
ERLC	Embryo Research Licensing Committee, a Principal Committee of NHMRC
Food and Drug Administration (FDA)	The Food and Drug Administration is the US Government agency responsible for public health and safety through control and supervision of human and animal drugs (medications), biological products and medical devices. The FDA also ensures the safety of food, cosmetics and other products.
Gamete	A mature haploid male (sperm) or female germ cell (egg) which is able to unite with another of the opposite sex in sexual reproduction to form a zygote.
Heteroplasmy	The situation where a cell, tissue or person contains more than one mtDNA genotype as opposed to the situation where all copies of the mtDNA are identical (homoplasmy). The term is commonly used where one type may lead to mitochondrial disease and the other does not.
Human Fertilisation and Embryology Authority (HFEA)	The Human Fertilisation and Embryology Authority is the UK's independent regulator overseeing the use of gametes and embryos in fertility treatment and research. The HFEA ensures that fertility clinics and research centres comply with the <i>Human Fertilisation and Embryology Act 1990</i> and the <i>Human Fertilisation and Embryology Act 2008</i> and provides guidance through the HFEA Code of Practice.
Homoplasmy	The situation where all copies of mtDNA in a cell, tissue or person are identical. All the mtDNA may be affected by a mutation leading to mitochondrial disease or all the mtDNA may be unaffected.
Maternal spindle transfer (MST)	A type of mitochondrial donation where an egg that has been constructed with nuclear DNA from the mother and mitochondria from the egg donor is fertilised with sperm from the father.
Mitochondria	Small energy-producing structures found within the cells of the body. They have a small amount of DNA (mitochondrial DNA) and are inherited only from the mother.
Mitochondrial donation	A technique involving the replacement of mitochondria within a cell or embryo. There are two main methods: maternal spindle transfer and pronuclear transfer. Also known as mitochondrial transfer or mitochondrial replacement.
Mitochondrial DNA (mtDNA)	Most DNA in a cell is in the chromosomes located in the nucleus. However, a small amount of DNA is located in the mitochondria. The genes in mtDNA encode proteins involved in mitochondrial enzymatic reactions or RNA molecules involved in protein synthesis. Unlike nuclear DNA, mtDNA is only inherited from the mother.

NHMRC	The National Health and Medical Research Council
NHMRC Act	<i>The National Health and Medical Research Council Act 1992</i>
Nuffield Council on Bioethics	An independent body in the UK that examines and reports on ethical issues in biology and medicine.
PHCR Act	<i>Prohibition of Human Cloning for Reproduction Act 2002</i>
Preimplantation genetic diagnosis (PGD)	A type of embryo screening used in ART prior to transfer of the embryo to a woman's uterus. The screening is used to identify embryos affected by a genetic condition. A small number of cells are removed (see 'embryo biopsy') and tested for the presence or absence of the mutation causing the condition.
Pronuclear transfer (PNT)	A type of mitochondrial donation where eggs from the mother and egg donor are fertilised with sperm from the father, and the nuclear DNA is removed from both resulting zygotes. The nuclear DNA from the donor/father zygote is discarded and replaced by the nuclear DNA from the mother/father zygote.
RIHE Act	<i>Research Involving Human Embryos Act 2002</i>
Somatic cell	Any cell of a multi-celled organism other than the reproductive cells (see gamete)
Zygote	A fertilised egg before the first cell division. It contains genetic material from the mother and father.

Relevant Sections of PHCR Act and RIHE Act

PHCR Act

8 Definitions

human embryo means a discrete entity that has arisen from either:

- (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or
- (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears;

and has not yet reached 8 weeks of development since the first mitotic division.

12 Offence—creating a human embryo for a purpose other than achieving pregnancy in a woman

- (1) A person commits an offence if the person intentionally creates a human embryo by a process of the fertilisation of a human egg by a human sperm outside the body of a woman, unless the person's intention in creating the embryo is to attempt to achieve pregnancy in a particular woman.

Penalty: Imprisonment for 15 years.

- (2) Despite subsection 13.3(3) of the *Criminal Code*, a defendant does not bear an evidential burden in relation to any matter in subsection (1) of this section.

13 Offence—creating or developing a human embryo by fertilisation that contains genetic material provided by more than 2 persons

A person commits an offence if:

- (a) the person intentionally creates or develops a human embryo by a process of the fertilisation of a human egg by a human sperm outside the body of a woman; and
- (b) the human embryo contains genetic material provided by more than 2 persons.

Penalty: Imprisonment for 15 years.

14 Offence—developing a human embryo outside the body of a woman for more than 14 days

A person commits an offence if the person intentionally develops a human embryo outside the body of a woman for a period of more than 14 days, excluding any period when development is suspended.

Penalty: Imprisonment for 15 years.

15 Offence—heritable alterations to genome

- (1) A person commits an offence if:
 - (a) the person alters the genome of a human cell in such a way that the alteration is heritable by descendants of the human whose cell was altered; and
 - (b) in altering the genome, the person intended the alteration to be heritable by descendants of the human whose cell was altered.

Penalty: Imprisonment for 15 years.

- (2) In this section:

human cell includes a human embryonal cell, a human fetal cell, human sperm or a human egg.

20 Offence—importing, exporting or placing a prohibited embryo

- (1) A person commits an offence if the person intentionally imports an embryo into Australia knowing that, or reckless as to whether, the embryo is a prohibited embryo.

Penalty: Imprisonment for 15 years.

- (2) A person commits an offence if the person intentionally exports an embryo from Australia knowing that, or reckless as to whether, the embryo is a prohibited embryo.

Penalty: Imprisonment for 15 years.

- (3) A person commits an offence if the person intentionally places an embryo in the body of a woman knowing that, or reckless as to whether, the embryo is a prohibited embryo.

Penalty: Imprisonment for 15 years.

- (4) In this section:

prohibited embryo means:

- (a) a human embryo created by a process other than the fertilisation of a human egg by human sperm; or
- (b) a human embryo created outside the body of a woman, unless the intention of the person who created the embryo was to attempt to achieve pregnancy in a particular woman; or
- (c) a human embryo that contains genetic material provided by more than 2 persons; or
- (d) a human embryo that has been developing outside the body of a woman for a period of more than 14 days, excluding any period when development is suspended; or
- (e) a human embryo created using precursor cells taken from a human embryo or a human fetus; or
- (f) a human embryo that contains a human cell (within the meaning of section 15) whose genome has been altered in such a way that the alteration is heritable by human descendants of the human whose cell was altered; or
- (g) a human embryo that was removed from the body of a woman by a person intending to collect a viable human embryo; or
- (h) a chimeric embryo or a hybrid embryo.

21 Offence—commercial trading in human eggs, human sperm or human embryos

- (1) A person commits an offence if the person intentionally gives or offers valuable consideration to another person for the supply of a human egg, human sperm or a human embryo.

Penalty: Imprisonment for 15 years.

- (2) A person commits an offence if the person intentionally receives, or offers to receive, valuable consideration from another person for the supply of a human egg, human sperm or a human embryo.

Penalty: Imprisonment for 15 years.

- (3) In this section:

reasonable expenses:

- (a) in relation to the supply of a human egg or human sperm—includes, but is not limited to, expenses relating to the collection, storage or transport of the egg or sperm; and
- (b) in relation to the supply of a human embryo:

- (i) does not include any expenses incurred by a person before the time when the embryo became an excess ART embryo; and
- (ii) includes, but is not limited to, expenses relating to the storage or transport of the embryo.

valuable consideration, in relation to the supply of a human egg, human sperm or a human embryo by a person, includes any inducement, discount or priority in the provision of a service to the person, but does not include the payment of reasonable expenses incurred by the person in connection with the supply.

22 Offence—creating a human embryo other than by fertilisation, or developing such an embryo

A person commits an offence if:

- (a) the person intentionally creates a human embryo by a process other than the fertilisation of a human egg by a human sperm, or develops a human embryo so created; and
- (b) the creation or development of the human embryo by the person is not authorised by a licence.

Penalty: Imprisonment for 10 years.

Note 1: The development of a human embryo outside the body of a woman for more than 14 days is prohibited by section 14.

Note 2: The placement in the body of a woman of a human embryo clone, or any other human embryo created other than by the fertilisation of a human egg by a human sperm, is prohibited by sections 9 and 20.

23 Offence—creating or developing a human embryo containing genetic material provided by more than 2 persons

A person commits an offence if:

- (a) the person intentionally creates or develops a human embryo by a process other than the fertilisation of a human egg by a human sperm; and
- (b) the human embryo contains genetic material provided by more than 2 persons; and
- (c) the creation or development of the human embryo by the person is not authorised by a licence.

Penalty: Imprisonment for 10 years.

Note 1: The development of a human embryo outside the body of a woman for more than 14 days is prohibited by section 14.

Note 2: The placement in the body of a woman of a human embryo created other than by the fertilisation of a human egg by a human sperm is prohibited by section 20.

RIHE Act

20 Person may apply for licence

- (1) A person may apply to the NHMRC Licensing Committee for a licence authorising one or more of the following:
 - (a) use of excess ART embryos;
 - (b) creation of human embryos other than by fertilisation of a human egg by a human sperm, and use of such embryos;
 - (c) creation of human embryos other than by fertilisation of a human egg by a human sperm that contain genetic material provided by more than 2 persons, and use of such embryos;

- (d) creation of human embryos using precursor cells from a human embryo or a human fetus, and use of such embryos;
 - (e) research and training involving the fertilisation of a human egg by a human sperm up to, but not including, the first mitotic division, outside the body of a woman for the purposes of research or training in ART;
 - (f) creation of hybrid embryos by the fertilisation of an animal egg by a human sperm, and use of such embryos up to, but not including, the first mitotic division, if:
 - (i) the creation or use is for the purposes of testing sperm quality; and
 - (ii) the creation or use will occur in an accredited ART centre.
- (1A) To avoid doubt, paragraphs (1)(a), (b), (c) and (d) do not permit the NHMRC Licensing Committee to authorise any use of an excess ART embryo or other embryo that would result in the development of the embryo for a period of more than 14 days, excluding any period when development is suspended.
- (2) An application under subsection (1):
- (a) must be made in accordance with the requirements (if any) specified in writing by the NHMRC Licensing Committee; and
 - (b) must be accompanied by the fee (if any) prescribed by the regulations.