



Australian
Academy *of* Health and
Medical Sciences

Submission to the NHMRC consultation on Mitochondrial Donation

FROM THE AUSTRALIAN ACADEMY OF SCIENCE AND
THE AUSTRALIAN ACADEMY OF HEALTH AND MEDICAL SCIENCES
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Consultation response to the NHMRC on Mitochondrial Donation by the Australian Academy of Sciences and the Australian Academy of Health and Medical Sciences, November 2019

The Australian Academy of Science (AAS) and the Australian Academy of Health and Medical Sciences (AAHMS) welcome the opportunity to respond to the consultation by the National Health and Medical Research Council on the 'Mitochondrial Donation Issues Paper: Ethical and Social Issues for Community Consultation'. This submission has been jointly prepared through input from Fellows of both Academies, alongside the AAS National Committee for Biomedical Sciences, National Committee for Medicine and Public Health, and National Committee for Cell and Developmental Biology, and Associate Members of AAHMS.

The Australian Academy of Science comprises more than 550 of the nation's most distinguished scientific practitioners. It has active groups of Fellows throughout Australia. It is extensively networked and is well balanced within and between the disciplines of science. The Australian Academy of Health and Medical Sciences (AAHMS) is the impartial, authoritative, cross-sector voice of health and medical science in Australia and an independent, interdisciplinary body of 399 Fellows – elected by their peers for their distinguished achievements and exceptional contributions to health and medical science in Australia.

Introduction and key messages

Mitochondrial diseases are conditions that can develop at different stages in life, with varying severity, for which there is typically no cure. Mitochondrial donation can offer prospective parents who are at high risk of passing on abnormal mitochondrial DNA that would cause devastating diseases, the possibility to conceive a genetically related child who is free of the disease. There are a range of safety, ethical, legal and regulatory considerations that need to be addressed in considering how such a technique might be implemented in practice.

Australian legislation currently prohibits the introduction of mitochondrial donation into clinical practice and also limits the scope of research on this topic. The Australian Academy of Science and Australian Academy of Health and Medical Sciences believe that there is now sufficient emerging evidence on the efficacy and safety of mitochondrial donation to explore the evaluation of these techniques in a clinical research setting in Australia, with appropriate regulation and consent, in specific circumstances. We would highlight the following points:

- **Mitochondrial donation should be introduced in a cautious and carefully regulated way. Initially limiting the technology to an appropriate clinical research setting will enable robust evaluation** of the technique in practice and the associated issues. These include, but are not limited to: informed consent, at-risk population screening, service delivery, cost, safety, community concerns, genetic and epigenetic consequences and impacts on individuals and families.
- Use of the technique should be **restricted to couples at high risk of having a child with severe mitochondrial DNA disease, where the balance of potential benefits over potential risks is compelling, and for whom there is no acceptable alternative way** to give them a chance of conceiving a genetically related child free of the condition.
- **Parents will need to be informed of the experimental nature of the technology**, including the potential risks and limitations, uncertainties around safety and efficacy. Consent from the potential parents will require discussion of all other reproductive options, including adoption, and the need for long-term follow up for themselves, their child and future generations. Potential parents would benefit from reproductive counselling.

- **Children born as a result of mitochondrial donation should have access to reproductive counselling and clinical follow-up** well into adult life, especially at critical milestones of development.
- **International exemplars provide useful frameworks for Australia to consider**, such as the approach taken by the Human Fertilisation and Embryology Authority (HFEA) in the UK, which incorporates strict regulatory and licensing conditions that require clinics conducting the treatment to be licensed and each case to be separately reviewed and approved by HFEA. The **National Health and Medical Research Council's (NHMRC) Human Embryo Research Licensing Committee (ERLC) is well placed to regulate clinical research on mitochondrial donation**. Research into these techniques should be allowed under certain circumstances, under appropriate regulation and oversight.

Responses to the consultation questions by the NHMRC:

1. Is it important to expand the options available to parents at risk of conceiving a child with mitochondrial disease by introducing mitochondrial donation into clinical practice in Australia?

The Issues Paper accurately summarises the options available to parents at risk of conceiving a child with mitochondrial disease. In so doing, it notes that for a small number of parents, faced with a specific set of circumstances likely to result in devastating disease, mitochondrial replacement therapy (mitochondrial donation) may represent the only option for them to have a chance of conceiving a genetically related child, free from mitochondrial disease. Ongoing research is required since further alternatives may be developed in the future and legislation should be amended to permit such research. However, there is a strong case for expanding the available options to include mitochondrial replacement for this small proportion of cases, particularly where preimplantation genetic testing of IVF embryos is not an option due to mutation load.

2. What risks and benefits are the most important to consider when thinking about the possible introduction of mitochondrial donation in Australia?

It is important that the risks and benefits are considered on a case-by-case basis, in the context of the severity of the disease and the certainty of that disease developing. If there is a high risk of severe disease, then mitochondrial transfer may be desirable – a risk/benefit analysis in such cases could lead parents to conclude that even if there are some significant risks, they are likely to be less than the disease itself, and therefore to proceed with mitochondrial transfer. As outlined under question 1 and in the Issues Paper, this is likely to apply in only a small number of cases – but in those cases, the technique could have life-changing consequences for families, reducing the emotional and financial impacts of severe disease. If there is lower expected harm from these diseases, the risk/benefit profile of mitochondrial replacement will shift, making the technique less desirable to parents.

Access should therefore be restricted to couples at high risk of having a child with severe mitochondrial DNA disease, where the balance of potential benefits to potential risk is high.

3. How can the interests and wellbeing of the child (and future adult) who may be born as a result of mitochondrial donation best be promoted and protected when considering the introduction of this new technology?

Mitochondrial diseases can have devastating effects on the wellbeing of children and their families. Mitochondrial donation may offer some parents a pathway to having genetically related children free from mitochondrial diseases. While the rights of the child are complex, as outlined in the Issues Paper,

one of the most significant rights of the child is to be free from a potentially catastrophic disease. However, the effects on a child born through mitochondrial donation (and future generations) are not yet known and must be carefully considered based on the latest knowledge. If introduced into clinical practice, the long-term impacts on these individuals will need to be understood.

After a comprehensive evaluation of risks and efficacy of mitochondrial donation techniques, the Human Fertilisation and Embryology Authority (HFEA) in the UK recommended that mitochondrial donation techniques (specifically maternal spindle transfer and pronuclear transfer) were sufficiently safe to be “cautiously introduced into clinical practice in specific circumstances”.¹ The technology should be introduced in a cautious and carefully regulated way, similar to the UK and as stated previously, access should be restricted to couples at high risk of having a child with severe mitochondrial DNA disease, where the balance of potential benefits to potential risk is high. Mitochondrial donation techniques should only be performed in a limited setting where health professionals and laboratory technicians are appropriately trained and skilled, which may mean that these techniques are only offered by one or two clinics in the first instance.

The novelty of this technique, which is still in the very early stages of human trials, demands close monitoring and scrutiny. Although there are ethical considerations to following up children (and future adults), many of which are outlined in the Issues Paper, there are also duties and responsibilities around the development of new therapies and techniques, which cannot be ignored. From a clinical perspective, following up outcomes for trial and research participants, which can often be needed throughout an individual’s lifetime, is critically important. It is also routine, as has been the case for many years for other reproductive technologies. For example, research continues to help better understand the consequences for individuals born through IVF – and has done so since it was first introduced into clinical practice more than 40 years ago. Studies in Australia, for instance, have involved children and those who are now adults.² In summary, it will be important to strike a balance – we must ensure there is adequate follow up, while also managing the ethical challenges and avoiding medicalising the child; an approach similar to the UK would be desirable, in which wherever possible the opportunity to follow up is taken during the regular health checks offered to every child.

It is critical that children born as a result of mitochondrial donation have access to clinical follow-up well into adult life – particularly focusing on critical time points/milestones of development – and reproductive counselling at an appropriate point. A comprehensive assessment could include: health related quality of life; transition to school, adolescence and adult life; and mental health and wellbeing, in addition to core medical and neurodevelopment outcomes. Care will be needed in establishing a system for recording and monitoring births, which retains privacy while also enabling appropriate follow up of the individual and evaluation of the technique – whether through a register of births, modifications to existing central IVF registers, or otherwise. It will also be important to consider how this important long-term follow up will be funded.

An important protection here relates to openness and transparency regarding the technique, particularly for those seeking to use it. If introduced into clinical research, prospective couples must be made aware of other reproductive options and any uncertainties around safety and efficacy. As outlined on P. 23 of the Issues Paper, they must have access to detailed, accurate, contemporary and relevant information

¹ HFEA (2016). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update. https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf. Accessed November 2019.

² For example: Novakovic, B. et al. (2019). Assisted reproductive technologies are associated with limited epigenetic variation at birth that largely resolves by adulthood. *Nature Communications* volume 10, Article number: 3922 (2019).

on the technique and the alternative options, which should include information about known risks and the potential for unknown risks. They should be encouraged to engage in long-term follow up of the child. Ahead of the treatment, there is also a need for appropriate screening of the health status of the potential mother and the egg donor, while providing equitable access to the technology.

It is also important to note that while IVF has been used in large numbers of individuals, enabling thorough evaluation of long-term safety, the numbers here will be small. This will impact on researchers' ability to assess the technique, especially if they wish to look at the different kinds of mitochondrial diseases.

4. What implications of mitochondrial donation for future generations are the most important to consider?

According to current evidence, mitochondrial donation is likely to increase the probability of having a child who is not affected by mitochondrial disease. However, transgenerational effects and possible heritable conditions need to be carefully considered (which may include unknown unknowns such as communicable diseases).³ Though the child could benefit from living a life without mitochondrial disease, it is possible that mitochondrial donation may carry unknown heritable changes and long-term follow-up will be essential to understand these. One of the most significant implications to consider is whether any of the potential safety concerns that have been raised (mitochondrial DNA reversion, haplogroup mismatching and epigenetic modification) pose any actual health risks for the child or their descendants. There should be ongoing research using animal models and collecting human data to determine whether any small amounts of mutant mitochondrial DNA carried over in to the embryo remain at a constant level in accessible body fluids and tissues and whether the individuals show any phenotypes that could be related to use of the technology.

Some of those concerned about the effectiveness of mitochondrial donation suggest that the selection of male embryos, created by mitochondrial donation, may help prevent donated mitochondrial DNA being passed onto the subsequent generation. As the Issues Paper points out, this not only raises safety and ethical concerns, but adds further complexities and inefficiencies to the treatment while potentially compromising the embryo's development. The approach was not supported by the HFEA in the UK because it would require preimplantation genetic testing, which meant "an additional step that is likely to compromise early development of already manipulated embryos; moreover, it would (on average) immediately reduce by half the number of embryos available for transfer".⁴ Other experts have pointed out that non-invasive PGD approaches to sex-selection using, for example, sampling of culture fluid, could minimise these concerns. Allowing mitochondrial donation into clinical research or clinical practice could offer future generations of women who were conceived through mitochondrial replacement the possibility of having their own biologically related children without passing on unhealthy mitochondrial DNA. The UK HFEA noted that "the subsequent use of PGD in this next generation, to select embryos with very low or no levels of abnormal mtDNA, may rid all subsequent generations of the need to have interventions to avoid mitochondrial disease".⁵

³ Note: There are some viruses that can be spread by mitochondrial transfer, although reported in animal studies (not humans) e.g. porcine respiratory virus. For example: Guo R, *et al.* (2018) Intercellular transfer of mitochondria rescues virus-induced cell death but facilitates cell-to-cell spreading of porcine reproductive and respiratory syndrome virus. *Virology*; 517: 122-134: <https://doi.org/10.1016/j.virol.2017.12.018>. Accessed November 2019.

⁴ HFEA (2016). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update. https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf. Accessed November 2019.

⁵ Ibid.

5. Are there ethical issues for the status of embryos in mitochondrial donation that are distinct from those for existing reproductive technologies such as IVF?

There may be additional ethical concerns in mitochondrial donation regarding inheritable genetic modifications that are beyond concerns around IVF. Nevertheless, many of the ethical issues for embryos in mitochondrial donation are consistent with those for existing reproductive technologies, which are already subject to high standards of regulation. Including mitochondrial donation in existing frameworks such as the NHMRC Ethical guidelines on the use of assisted reproductive technology in clinical practice and research (ART Guidelines) would be a matter of inclusion of a new category, rather than wholesale redrafting. Specifically, inheritable genetic modification is illegal in humans based on current legislation. Since mitochondrial donation includes an inheritable genetic modification in genetic descendants, legislative change or exceptionalism will be required to introduce this technology in Australia. In the UK, an exception to the consensus definition of inheritable genetic modification was used to allow mitochondrial donation.

The precedents set by approving or obstructing the use of mitochondrial donation in Australia will have other implications for the use of techniques that involve inheritable genetic modification. These should be considered and specifically addressed in any approval of mitochondrial replacement.

6. Are there ethical issues for women who donate eggs for mitochondrial donation that differ from other current assisted reproductive technologies?

Treating mitochondrial donation as an extension of existing reproductive technologies will mean existing structures can be adapted and used. The NHMRC's ethical guidelines on the use of assisted reproductive technology in clinical practice and research addresses the often complex considerations regarding the interests of the prospective parents, embryo and sperm donors. The guidelines also address a range of possible implications for embryo (and sperm) donors. Some of these considerations include psychological implications (including counselling for donors and parents), awareness of risks, privacy, consent.⁶ Ethical treatment of women who donate eggs for mitochondrial donation can be approached as an extension of current practices for assisted reproductive technologies, rather than a wholly new consideration. This will require consideration of issues such as whether to provide access to information about the woman who was the egg donor and how to deal with cases where egg donors discover that they themselves have a disease-causing mitochondrial mutation. As indicated in the Issues Paper, although some would argue that the contribution of organelles and mitochondrial DNA differs substantially from that associated with donation of gametes (and the inheritance of traits from the egg donor), it is possible that children born of mitochondrial donation may wish to have a connection with the egg donor in the future. Privacy and consent issues remain of high importance to potential donors.

7. If mitochondrial donation is introduced into clinical practice, who should be allowed to access mitochondrial donation? Who should decide who has access in specific cases? What conditions, if any, should be imposed on patients and clinicians?

If legislative change is introduced in Australia, research, training and clinical use must be reviewed and approved on a case-by-case basis, and the application should be undertaken in a clinical research setting

⁶ National Health and Medical Research Council (2017). Ethical guidelines on the use of assisted reproductive technology in clinical practice and research. Canberra: National Health and Medical Research Council.

in the first instance. Clinical need should be the main consideration for access to mitochondrial donation. The Academies recommend adopting a two-phase approach as implemented by United Kingdom's Human Fertilisation and Embryology Authority (HFEA) – in which the first phase involves licensing of IVF clinics with specialist skills in mitochondrial donation and relevant ART techniques, and the second requires full review of each application.

In Australia, accreditation by the Reproductive Technology Accreditation Committee (RTAC) is required for use of any ART application. Accreditation from RTAC requires ART clinics to comply with ART laws and the related guidelines. Similar standards must also apply to facilities for mitochondrial donation.

The National Health and Medical Research Council's Human Embryo Research Licensing Committee (ERLC), which has been responsible for the oversight of research involving the use of human embryos since 2002, is well placed to regulate research on mitochondrial donation on a case-by-case basis. It may be that additional expertise specific to mitochondrial donation would be welcomed. With extended functionality of clinical and scientific evaluation specifically for mitochondrial donation, the ERLC is an appropriate regulatory body for oversight of mitochondrial donation research. The ERLC could also oversee a publicly available database containing information about licences issued and outcomes, as well as regular reporting to the Parliament of Australia.

For some diseases, it will take many years to know whether the treatment has been successful. For example, in the case of the mitochondrially inherited eye disease known as Leber Hereditary Optic Neuropathy, which results in severe visual impairment, onset usually occurs in young adulthood (but can be even later).

8. Having considered the issues outlined in this paper and your answers to the previous seven questions, would you support the introduction of mitochondrial donation to prevent the transmission of severe mitochondrial DNA disease at this time?

Health and medical research should aim to benefit patients and the community by reducing disease and promoting health. Based on the best available scientific evidence at this stage, mitochondrial donation is likely to substantially lower the risk of mitochondrial disease, which for those affected can be severely disabling and, in some cases, can cause death at a young age or in adulthood.^{7,8} We would support the use of mitochondrial donation in a clinical research setting under circumstances similar to those applied in the UK, where there is a well-documented and appropriate clinical path. As outlined previously, it would be restricted to couples for whom there is a likelihood that inheritance of mitochondrial disease without intervention will cause death or serious disease, and for whom there is no acceptable alternative way to prevent inheritance of the condition. Informed consent comprising all reproductive alternatives and anticipated consequences will be paramount.

The circumstances in which it could be used would need to be clearly defined and the technique would need to be appropriately regulated and limited to core providers who comply to regulation set out by governments and scientific bodies. Public confidence in the regulatory model could benefit from oversight by an independent body, such as the NHMRC ERLC. This oversight would provide additional scrutiny to ensure that the methods used in a given centre and the level of expertise are appropriate. A model similar to the UK could again be considered here, where clinics conducting the treatment must be

⁷ Kang E, Wu J, Gutierrez NM, *et al.* (2016). Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. *Nature* 2016;540:270-275

⁸ Hyslop LA, Blakeley P, Craven L, *et al.* (2016) Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. *Nature* 2016;534:383-386

licensed by the HFEA, and each case must be reviewed and approved by HFEA. Only centres with recognised expertise in the embryology, mitochondrial DNA genetics, counselling and support should be licensed to offer the technology. Initial introduction would therefore be in one or a very limited number of centres.

Another risk that warrants consideration is that if the technique is not made available in Australia, then some parents will likely travel overseas, as we have seen with patients pursuing unproven stem cell treatments.

9. If Australia did decide to change the law to allow mitochondrial donation, how important would it be to limit its use initially to research studies? Would it be appropriate to introduce it directly into clinical practice?

It would not be appropriate to introduce the technique directly into clinical practice in the first instance. In 2016, the UK HFEA recommended that “it is appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients”.⁹ They noted that a number of potential safety risks were considered to be small, but they have not been definitively excluded.¹⁰ Therefore, if Australian legislation was to allow mitochondrial donation, it should be initially limited to a clinical research setting, to ensure that optimal data can be collected and published about safety and efficacy, and associated issues such as service delivery, cost, safety, and impacts on individuals and families.

Although Australia is able to benefit from the research findings from the UK, there are privacy limitations around what can be shared from their most recent work. It would therefore be beneficial to generate clinical evidence in the Australian context to make it possible for Australians who are at high risk of passing on unhealthy mitochondrial DNA to benefit from these new techniques, and to give our own citizens access to these sorts of cutting edge treatments. Australia has world-leading expertise to contribute on this topic and it would be valuable globally if we as a nation were contributing to the evidence-based research on mitochondrial donation. An active research sector might engender a research-sharing agreement with UK researchers to allow Australian researchers to access confidential research results.

It would be worth exploring whether the relevant Australian authorities may be able to receive briefings in confidence from colleagues in the UK who are using these techniques, which are understandably subject to privacy and confidentiality at this stage, to seek insights to the latest understanding of their application in practice.

If introduced into a clinical research setting, patients will need to be informed of the experimental nature of procedures involved in mitochondrial donation, including the potential risks and limitations. Patients will also need to be made aware of the importance of long-term follow up (involving themselves and their offspring, potentially for generations), which is required to build the evidence base and safe practice of mitochondrial donation. It should be noted that the Australian medical research sector has well-established instruments to allow and promote ethical research practices, including a strong legislative framework, robust ethical oversight, and world-leading guidelines covering research in humans. Potential parents would also benefit from reproductive counselling.

⁹ HFEA (2016). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update. https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf. Accessed November 2019.

¹⁰ Ibid.

10. Does this paper explore the relevant ethical and social considerations associated with the introduction of mitochondrial donation? Are there any additional ethical or social issues that need to be considered?

The paper explores some of the most immediate ethical and social considerations that are associated with the introduction of mitochondrial donation.

Some of the additional considerations include:

- Safeguarding patients from potential cost exploitation and ensuring equitable access. Treatment would ideally be available at a low cost or with cost recovery available.
- Considering the genetic relationship between the mitochondria donor and the child conceived through mitochondrial donation.

We are grateful to the Fellows and Associate Members who contributed to this response. For further information about this response, please contact Dr Stuart Barrow, Senior Policy Analyst at the Australian Academy of Science (stuart.barrow@science.org.au) or Katrin Forslund, Policy and Projects Officer at the Australian Academy of Health and Medical Sciences (katrin.forslund@ahms.org).