Chapter 5

Regulation

Introduction

5.1 The previous chapters of this report have examined evidence on the safety, efficacy and ethical considerations of using mitochondrial donation to reduce the chance of a mother passing on mutated mitochondrial DNA (mtDNA) to a child, potentially leading to mitochondrial disease.

5.2 The issue that remains to be examined is what legislative amendments would need to be made if mitochondrial donation was to go ahead. The most evident place to start, is to look to the example set in the United Kingdom (UK).

UK path to regulation

5.3 As outlined in previous chapters, in 2015 the UK Parliament passed regulations to legalise mitochondrial donation for women with a high chance of passing on mitochondrial disease to their children. The change to law authorised the regulation of mitochondrial donation to be undertaken by the Human Fertilisation and Embryology Authority (HFEA), as the UK’s independent regulator of fertility treatment and research using human embryos. Some research has suggested that having an agency dedicated to fertility and embryology has assisted the UK to make advances in this field.

5.4 The new UK regulations require that a licence from the HFEA for mitochondrial donation is needed for the clinic administering the treatment, as well as for individual women seeking treatment. As of 30 April 2018, the HFEA Statutory Approvals Committee has considered six applications from individual women to access mitochondrial donation treatment. Minutes for three applications have been published: two were approved and the third was rejected pending more information showing that alternative options available to the patient were not suitable.

5.5 As shown by the above HFEA approvals process, access to the treatment is highly restricted and it is not anticipated that access requirements will be relaxed in the foreseeable future.

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1 Deoxyribonucleic acid.
2 Human Fertilisation and Embryology Authority (HFEA), Submission 53, p. 1.
3 National Health and Medical Council (NHMRC), Submission 4, p. 5.
4 The HFEA Statutory Approvals Committee is supported by an international panel of experts in mitochondrial disease, including Professor David Thorburn. This panel conducts peer review of applications.
5.6 As a first stage prior to clinical use, the HFEA reconvened its expert advisory panel to advise on whether science suggested mitochondrial donation was sufficiently safe to be offered in treatment. It was ultimately decided that the science was safe enough for carefully limited application. Secondly, the HFEA established a regulatory regime to oversee how and when those licences would be issued.

5.7 The HFEA established a detailed Code of Practice for the use of mitochondrial donation and its Statutory Approvals Committee was authorised to approve access to treatment on a case-by-case basis as 'a clinical risk reduction treatment for carefully selected patients'.

5.8 The HFEA Code of Practice covers issues such as:

- the consent process;
- the information required to be provided to the participants;
- 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, and
- the requirement to report to the HFEA if the clinic becomes aware of any adverse outcomes following treatment involving mitochondrial donation.

5.9 The UK regulations allow for mitochondrial donation to be undertaken for a couple at serious risk of passing on severe mitochondrial disease. While no specific definitions have been outlined in the regulations, the determination of what is considered 'serious risk' of 'severe mitochondrial disease' is ultimately determined by the licensing panel at the HFEA. In practice, the Australian Mitochondrial Disease Foundation (AMDF) submitted that 'severe' is generally considered to be a condition which would have an early onset in a child's life and significantly impact their day-to-day functioning and quality of life. It may, but would not necessarily, be life-limiting.

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6 NHMRC, Submission 4, p. 4.
7 NHMRC, Submission 4, pp. 4–5.
8 Australian Mitochondrial Disease Foundation (AMDF), Submission 26.1, p. 4.
5.10 To support an application for a licence for an individual to undergo mitochondrial donation, a clinic must provide patient-specific information, including:

- the patient's medical history;
- the patient's mutant mtDNA load;
- the patient's family medical history of the mtDNA mutation or disease;
- scientific literature relevant to the mtDNA mutation or disease, and
- any additional information which the clinician may consider is relevant to the application.

5.11 The Murdoch Children's Research Institute submitted that in creating a flexible regulatory regime overseen by an expert government body 'the UK Parliament recognized that developing detailed legislation to regulate all aspects of the mitochondrial donation process was impractical and they devolved much of this responsibility to the HFEA to determine exactly when and how mitochondrial donation would be delivered in the UK'.

5.12 The majority of submitters and witnesses to this inquiry recommended a cautiously staged introduction of mitochondrial donation in Australian clinical practice, based on the findings of the HFEA in the UK that mitochondrial donation is sufficiently safe to be introduced into clinical practice in specific circumstances. The AMDF submitted:

> The rigour and depth of the reviews and process undertaken in the UK should provide the Senators with the confidence that mitochondrial donation could be introduced into the Australian context. Whilst some of the regulations adopted in the UK may need to be adapted to align with Australia's specific expectations or current laws regarding IVF [or ART], they provide a strong basis from which to work towards offering Australian parents the capacity to access these techniques.

5.13 However, prior to examining whether the UK regulatory regime provides good examples for any Australian regulation, a definitional barrier remains, in that Australian anti-cloning legislation as it is currently drafted prohibits this technique. This issue is discussed below.

**Australian legislative prohibitions on germline modification**

5.14 The main legislative barrier to mitochondrial donation is the blanket prohibition on any form of germline genetic modification contained in the *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act).

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9 HFEA, *Submission 53—Attachment 1*, pp. 4–5.

10 Murdoch Children's Research Institute and Victorian Genetic Clinical Services (Murdoch Children's Research Institute), *Submission 23*, p. 8.

5.15 There are three relevant provisions within the Cloning Act: section 13 prohibits the creation of a human embryo outside the body of a woman which contains genetic material from more than 2 persons and section 20 prohibits placing such an embryo into a woman. Section 15 prohibits the alteration of the genome of a human cell where that alteration is inheritable.

5.16 However, as discussed in chapter four, evidence to the committee is that many submitters and witnesses do not consider mitochondrial donation as a traditional germline (inheritable) genetic modification. While there was some distinction between how different witnesses characterised it, most agreed that mitochondrial donation was a new form of genomic modification and should be treated as such. Associate Professor Catherine Mills, a philosopher and bioethicist at Monash University, told the committee that because current legislative prohibitions were 'formulated prior to the possibility of mitochondrial donation, it's now time for it to be reconsidered.'12

5.17 This approach accords with the UK regulations allowing for mitochondrial donation, which classified the treatment as germline modification, but not genetic modification.13

5.18 The Human Genetics Society of Australasia submitted that 'ethical reviews in the UK and USA have also recognised that…mitochondrial donation is distinct from germline genetic modification and should not be prevented based on false equivalency arguments.'14

5.19 Bioethicist Dr Ainsley Newson characterised mitochondrial donation as a novel class of 'conditionally inheritable genomic modifications' and advised:

> The conditional inheritance of mitochondrial donation makes it conceptually distinct from other inheritable (or germ-line) genetic modifications. This means its automatic prohibition on this ground is not warranted.15

5.20 A simple approach to eliminating the legislative restrictions was suggested by the National Health and Medical Research Council (NHMRC) as amending legislation:

> …so that mtDNA was not included when determining how many people had contributed genetic material to an embryo (PHCR [Cloning] 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.16

5.21 Academics from Monash University put forward a similar suggestion, that:

12 Associate Professor Catherine Mills, Committee Hansard, 17 May 2018, p. 50.
13 Associate Professors Mills and Karinne Ludlow, Professor Robert Sparrow and Dr Narelle Warren, Submission 20, p. 6.
14 Human Genetics Society of Australasia, Submission 2, p. 2.
15 Associate Professor Ainsley Newson, Submission 29, p. 3.
16 NHMRC, Submission 4, p. 7.
The most straightforward legal route would be to treat mitochondrial DNA as separate from the human genome. This approach parallels the UK process and resonates with existing legislation of embryos and cloning, as well as current legal definitions of genetic material and the genome, which are highly opaque.\textsuperscript{17}

5.22 However, the submission goes on to state that key definitional issues must be resolved before legislation can be developed around mitochondrial donation, including:

- whether this technology constitutes genetic modification / gene technology according to current definitions;
- whether it can be considered either germline or somatic modification, and whether this distinction remains useful; and
- how mitochondrial and nuclear DNA should be defined and regulated.\textsuperscript{18}

5.23 Dr Newson submitted that mitochondrial donation is a good example of how 'black letter law' can be an imperfect instrument for regulating emerging reproductive technologies and that regulatory instruments such as the genetic privacy regulations under the \textit{Privacy Act} (Cth) have more flexibility for change than primary legislation.\textsuperscript{19}

5.24 The Human Genetics Society of Australasia concurred with this view, and submitted:

> We would strongly advocate for a flexible and adaptive system of governance, to help avoid the problems that have come from the existing regulatory regime; in particular there being no further reviews required to the cloning/embryo laws. This and similar areas of reproductive science are fast-moving; and regulation needs to be similarly flexible and adaptive.\textsuperscript{20}

\textit{Committee view}

5.25 As outlined in chapter four, the committee recognises the majority of the evidence presented that mitochondrial donation is not considered a form of germline genetic modification as envisioned by Australian laws which prohibit cloning and other similar forms of genetic modification.

5.26 However, the committee remains of the belief that it does not have the required expertise to make such a determination, and notes a formal determination must be taken by an appropriate body with the relevant expertise. If this view is confirmed, then appropriate amendments should be made to Australian law to keep it up-to-date with science and to allow for, and only allow for, mitochondrial donation.

\textsuperscript{17} Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, \textit{Submission 20}, p. 5.
\textsuperscript{18} Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, \textit{Submission 20}, p. 5.
\textsuperscript{19} Associate Professor Newson, \textit{Submission 29}, p. 5.
\textsuperscript{20} Human Genetics Society of Australasia, \textit{Submission 2}, p. 3.
Australian approach to introduction

5.27 As outlined earlier in this chapter, the UK process is similar to an Australian clinical trial process,\(^{21}\) which is overseen by the NHMRC,\(^{22}\) or the regulation of medical therapies with restricted access such as the Life Saving Drugs Program, where a clinician must submit medical evidence on a patient's health condition which is evaluated by a panel of experts prior to any approval to access the medication.\(^{23}\)

5.28 The NHMRC submitted that there are two paths by which mitochondrial donation could be introduced into Australia. The first would be to follow the process undertaken in the UK, by allowing a small number of centres in Australia to conduct research, validation and training activities, which include the creation and destruction of human embryos, prior to any clinical use. A second option, allowing immediate clinical use but prohibiting the creation of embryos for research, training and validation, would mean that children 'born following the first use of mitochondrial donation in Australia would bear the increased risk associated with establishing expertise in the new technique'.\(^{24}\)

5.29 The NHMRC recommended that if mitochondrial donation is to be allowed in Australia, it should first be conducted within a research context—or clinical trial—to increase the evidence base for the safety and efficacy of this technique.\(^{25}\)

5.30 An Australian introduction was generally seen by submitters as a two-pronged approach of allowing almost immediate access to the treatment for a limited number of women (potentially as a clinical trial) as soon as a clinic demonstrated the required expertise in administering the treatment, and at the same time allowing for additional research to be undertaken.\(^{26}\) Any clinical use of mitochondrial donation would of course require legislative amendments as described above.

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\(^{21}\) A clinical trial usually involves a double-blind study of the efficacy of a treatment or medication, which would not be appropriate in the context of mitochondrial donation. Notwithstanding this, the term clinical trial is useful for a layperson to conceptualise the limitations that would be placed on accessing mitochondrial donation if introduced in a controlled manner to Australian clinical practice. An appropriate description would be an observational clinical trial.


\(^{24}\) NHMRC, *Submission 4*, p. 6.

\(^{25}\) NHMRC, *Submission 4*, p. 6.

\(^{26}\) An approach to allow immediate limited clinical application of mitochondrial donation was recommended by the following key organisations: Australian Academy of Science, *Submission 35*, p. 2; AMDF, *Submission 26*, [p. 12]; Fertility Society of Australia (Fertility Society), *Submission 27*, p. 3; Monash Biomedicine Discovery Institute, *Submission 19*, [p. 3]; Murdoch Children's Research Institute, *Submission 23*, p. 2 as well as a number of individual clinicians and researchers with specialities in mitochondrial disease.
Committee view

5.31 The committee considers that a limited clinical trial should be considered before full introduction of mitochondrial donation and that additional research could be simultaneously conducted. The committee notes that medical trials would require a change of legislation before they could proceed.

Australian regulatory regime

5.32 Most submitters and witnesses in favour of mitochondrial donation put forward the UK system as a good basis for a regulatory system in Australia, with some modification.27

5.33 The Genetic Support Network of Victoria stressed the importance of well-planned implementation managed by experts:

Implementation is very important. It will require responsible and very clear messaging that will be based on a very clear decision. We need a clear and effective regulatory environment to support mitochondrial donation and we need to allow our clinical experts to do the job.28

5.34 AMDF submitted that 'the UK regulatory process reflects significant work and effort over many years in its development and, whilst some tweaking may need to occur, Australia already has a framework in existence that could be adapted to address and regulate mitochondrial donation'.29

5.35 A common recommendation was to use the current Australian system for regulating both human embryo research and Assisted Reproductive Technology (ART) clinics. This would entail the Embryo Research Licensing Committee (Licensing Committee) of the NHMRC to be responsible for the licensing of centres and individuals seeking treatment, and the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (Fertility Society)30 to have a role in providing advice on the clinical capacity of ART clinics to provide this service.

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27 See for example AMDF, Submission 26, [p. 9]; Australian Academy of Science, Submission 35, p. 7; Biomedical Ethics Research Group, Murdoch Children's Research Institute, Submission 34, [p. 4]; Fertility Society, Submission 27, p. 2; Human Genetics Society of Australasia, Submission 2, p. 4; Monash Biomedicine Discovery Institute, Submission 19, [p. 2]; Murdoch Children's Research Institute, Submission 23, p. 2; Progress Educational Trust, Submission 48, p. 2; Wellcome Centre for Mitochondrial Research, Submission 45, [p. 6].

28 Ms Monica Mary Ferrie, Chief Executive Officer, Genetic Support Network of Victoria, Committee Hansard, 17 May 2018, p. 2.

29 AMDF, Submission 26.1, [p. 10].

30 The Embryo Research Act requires all Assisted Reproductive Technology (ART) clinics to be accredited by the Reproductive Technology Accreditation Committee of the Fertility Society, which regulates and licences the 88 ART clinics across Australia.
as well as an ongoing compliance monitoring role of clinics in collaboration with the Licensing Committee.  

5.36 The Licensing Committee of the NHMRC was seen to be the most suitable body to regulate licences, as it is has been responsible for the oversight of research involving the use of human embryos for 15 years, and is well placed to regulate research of mitochondrial donation on a case-by-case basis. The Murdoch Children's Research Institute submitted that there may be greater public confidence in the regulation of mitochondrial donation if the licences were granted by a body that is independent of the ART industry, such as the NHMRC, but suggested that '[i]f this was unsuitable then it may require an independent body to be set up, perhaps with input from the Australian Academy of Health and Medical Sciences.'  

5.37 The Australian Academy of Science further recommended the NHMRC 'oversee a publicly available database containing information about licences issued and outcomes, as well as regularly report to the Parliament of Australia.'  

5.38 A submission from a coalition of professors with expertise in mitochondrial disease noted that the current NHMRC Licensing Committee did not include a member with substantive clinical or scientific expertise in mitochondrial disorders and suggested 'a person with that expertise may be needed to supplement the committee's existing skills in embryology, ART technologies, ethics and community representation'.  

5.39 The RTAC of the Fertility Society submitted they would be able to include the regulation of mitochondrial donation in their current regulatory framework: RTAC is the accrediting body for ART in Australia, and would therefore take on clinic accreditation of this technique. If further legislative oversight was deemed necessary, the NHMRC embryo research licensing committee could require ART clinics to seek accreditation. These levels of controls would see that Mitochondrial transfer was conducted in the most stringent manner to ensure optimal outcomes for the families at risk and society in general.  

5.40 The majority of submitters were supportive of replicating the double-licensing system used in the UK, where both the clinic and the patient must have a licence prior to the use of mitochondrial donation. Professor Christodoulou outlined how this could work in practice:

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31 This model was supported by Australian Academy of Science, Submission 35, p. 7; Fertility Society, Submission 27, p. 2; Murdoch Children's Research Institute, Submission 23, p. 13, among others.
33 Australian Academy of Science, Submission 35, p. 7.
34 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan, Aleksandra Filipovska, Submission 59, p. 2.
35 Fertility Society, Submission 27, p. 2.
Firstly, one wants to be confident that the organisation that's going to be offering the IVF technology has the skill set and expertise to be able to do that. That would require expert panels to review the scientific and clinical credentials of whatever the organisation was…

And then the second aspect of the licensing—and this is very much following the UK model—is that one needs to be really careful about identifying for which families this technology will truly be of benefit. That would require the evaluation by an expert panel—which I would suggest should include both paediatric and adult mitochondrial specialists, IVF specialists, geneticists and, importantly, community representation as well—to identify on a case-by-case basis those individuals who would truly benefit by having mitochondrial donation versus others who might be better potentially directed towards traditional prenatal testing or preimplantation genetic diagnosis or where none of these technologies may be relevant.

5.41 There were a number of additional regulatory issues that were recommended by submitters and witnesses as important components to a regulatory regime that protected the safety and well-being of parents using mitochondrial donation, children born of this technique and potential donors. These are examined below.

**Restrict purpose to mitochondrial disease**

5.42 The clinical purpose of mitochondrial donation was discussed by multiple submitters and witnesses. Beyond preventing mitochondrial disease, mitochondrial donation has been tested as a treatment for certain infertility issues, and recent medical research has indicated that mtDNA mutations are implicated in many further health problems, such as diabetes, autism and some inheritable cancers. Mitochondrial donation may well prove, at some unknown point in the future, to be a viable prevention treatment for health conditions beyond mitochondrial disease.

5.43 However, there was a universal view that while mitochondrial donation was still in its early years and is somewhat experimental, the unknown risks may be acceptable to take for reducing the generational transmission of severe mitochondrial disease to children, but was not considered appropriate to take for other diseases or as an ART enhancement at this point in time.

5.44 Professor David Thorburn of the Murdoch Children's Research Institute recommended that limiting mitochondrial donation to preventing mitochondrial

36 Murdoch Children's Research Institute, Submission 23, p. 10.


38 This view was put by many submitters and witnesses, for example: AMDF, Submission 26, [p. 9]; Murdoch Children's Research Institute, Submission 23, pp. 13–14; Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories, Murdoch Children's Research Institute, Committee Hansard, 17 May 2018, p. 12; Professor John Christodoulou, Chair, Genomic Medicine, Department of Paediatrics, University of Melbourne, Committee Hansard, 17 May 2018, p. 13; Associate Professor Mills, Committee Hansard, 17 May 2018, p. 54; Associate Professor Newson, Committee Hansard, 17 May 2018, p. 54.
disease should be done in primary legislation. However, Professor Thorburn further noted that while mitochondrial donation should be 'ring-fenced' to the purpose of mitochondrial disease, there is still a degree of flexibility required in the assessment of how to implement that in practice:

I think it's impossible to put all the detail into the legislation. It's going to be quite complicated and it will be necessary to hand off—there's not exactly an equivalent of the Human Fertilisation and Embryology Authority in Australia, but it needs to be, to a degree, handed off to an expert independent committee to narrow down the details of how that can proceed in practice but be restricted to using it for mitochondrial DNA donation to prevent severe mitochondrial disease.

5.45 Dr Newson also argued for some flexibility on the grounds that women most likely to pass on the more serious forms of mitochondrial disease are often too sick to be able to use mitochondrial donation.

5.46 Associate Professor Catherine Mills agreed that it would be prudent to start with limiting access to those women most in need of this technology as 'women whose children would most clearly suffer from serious mitochondrial disease in the circumstance of not using the technology' and noted that the risks of this technology 'would still probably have lesser health impacts than the risks of mitochondrial disease'.

5.47 Further to this, the UK restricts mitochondrial donation to couples for whom pre-implantation genetic diagnosis (PGD) or other methods would be inappropriate or unlikely to succeed. As stated earlier in this chapter, a person seeking a licence in the UK must demonstrate that other methods for having children are not an option.

5.48 Professor Thorburn supported this position and told the committee that '[p]re-treatment assessment must take into account a range of factors and I also believe this should be overseen by a body independent of the ART industry, which could presumably be the same body overseeing licensing of centres, with input from experts in multiple disciplines'.

39 Professor Thorburn, Committee Hansard, 17 May 2018, p. 12.
40 Professor Thorburn, Committee Hansard, 17 May 2018, p. 17.
41 Associate Professor Newson, Submission 29, p. 5.
42 Associate Professor Mills, Committee Hansard, 17 May 2018, p. 54.
43 Murdoch Children's Research Institute, Submission 23, pp. 6, 14.
In practice, many submitters and witnesses pointed to the UK regulation regime as a good way to restrict access to mitochondrial donation through the dual licensing system.\textsuperscript{44}

\textit{Multiple donation techniques}

As outlined in chapter three, evidence suggests a preferred method of mitochondrial donation does not appear to have yet been identified. Consideration needs to be given to the way any possible regulation is framed to permit the safest and most up-to-date scientific techniques to be used in Australia.

Professor John Carroll from the Monash Biomedicine Discovery Institute noted that pronuclear transfer is the preferred method being investigated by the UK clinic licensed to undertake mitochondrial donation 'which gives me more confidence in being able to understand any technical details about making that as good as it possibly can be'. That being said, Professor Carroll recommended that both pronuclear transfer and maternal spindle transfer should be allowed for under any Australian regulatory regime, to 'give us the best flexibility and adaptability as we move forward through the process of learning how successful the technique is and how we can adapt it and improve it as will always happen in new techniques like this'.\textsuperscript{45}

Professor Carolyn Sue, Director of the Mitochondrial Disease Research Centre at the Kolling Institute of Medical Research, agreed and noted that if both techniques for mitochondrial donation were available, patients with an ethical objection to the destruction of embryos would be able to access the treatment.\textsuperscript{46}

Professor Justin St John, Head of the Mitochondrial Genetics Group at the Hudson Institute of Medical Research, presented evidence to the committee on new techniques for mitochondrial donation which uses eggs at an earlier development stage that currently used in maternal spindle transfer. This was discussed in detail in chapter three. Professor St John recommended that changes to law should be inclusive, to allow for scientific changes.\textsuperscript{47}

\textit{Clinical capacity and numbers}

The regulation of ART clinics offering mitochondrial donation in the UK is done by the HFEA. Professor Thorburn supported any Australian regulation to follow


\textsuperscript{45} Professor John Carroll, Director, Monash Biomedicine Discovery Institute, Monash University, \textit{Committee Hansard}, 17 May 2018, p. 25.

\textsuperscript{46} Professor Carolyn Sue, Director, Kolling Institute of Medical Research, Mitochondrial Disease Research Centre, \textit{Committee Hansard}, 17 May 2018, p. 27.

\textsuperscript{47} Professor Justin St John, Professor and Head, Mitochondrial Genetics Group, Hudson Institute of Medical Research, \textit{Committee Hansard}, 17 May 2018, p. 45.
the approach of the HFEA, which imposes 'a requirement for appropriate levels of skill being demonstrated by named practitioners within a named clinic, and relevant key performance indicators being met, parameters that will be assessed by the HFEA'.

5.55 Professor Thorburn recognised that regulation in Australia would be more complex than the UK method, as the clinical application of new ART techniques would need to be accredited by the RTAC of the Fertility Society.

5.56 Most people and organisations in favour of mitochondrial donation recommended that clinic numbers be limited in the initial stage, to allow for one or two centres of excellence to be established. The Human Genetics Society of Australasia also submitted this would 'aggregate relevant clinical experience, provide training, patient follow-up and clinical audit so as to support the greatest possible benefits to patients and healthy outcomes for children'.

5.57 Professor Sue told the committee that the capacity exists within Australian clinics to provide this treatment:

When I speak to IVF centres, there is an appetite for this technology transferral. There's no real concern about not being able to do it. It's more about changing the legislation to make it legal and also determining the demand for this procedure. I think the capability is there, the appetite is there, but the legislation doesn't allow us to do it at this stage.

5.58 Dr Petra Wale from the Fertility Society noted that mitochondrial donation would not be 'a routine offering on an IVF platform' and that limiting the numbers of clinics providing this treatment would create centres of excellence.

5.59 Professor Sue also discussed the number of clinics which should be initially licensed, and noted that while the UK had licensed only one clinic at this stage, the geographical spread of Australia meant that a 'tyranny of distance' could create equity and fairness issues for patients should only a single clinic be licensed in Australia.

Follow-up

5.60 AMDF pointed to the UK model for follow-up, where clinics offering mitochondrial donation must have a documented process for monitoring children born following mitochondrial donation, including medical follow-up, with mandatory reporting of any adverse events, such as birth defects, genetic abnormality or another

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48 Murdoch Children's Research Institute, Submission 23, p. 13.
49 Murdoch Children's Research Institute, Submission 23, p. 13.
50 Human Genetics Society of Australasia, Submission 2, p. 4.
51 Professor Sue, Committee Hansard, 17 May 2018, p. 24.
52 Dr Petra Wale, Board Member, Fertility Society, Committee Hansard, 17 May 2018, p. 27.
53 Professor Sue, Committee Hansard, 17 May 2018, p. 27.
adverse outcome such as a miscarriage. The Australian Academy of Science further recommended that haplotype information should also be collected.

5.61 Dr Nadine Richings, Vice Chair of Scientists in Reproductive Technology (SIRT) recommended rigorous follow-up similar to the procedures followed with the introduction of the ART process intracytoplasmic sperm injection, ICSI. Dr Richings informed the committee that:

If mitochondrial donation was permitted Australia, SIRT would support and recommended rigorous evaluations of laboratory outcomes and also follow-ups of any children born through these procedures. The Australia and New Zealand Assisted Reproduction Database, ANZARD, could report this information. The purpose of ANZARD is to collect, monitor and monitor the perinatal outcomes of assisted reproduction and to assess the effectiveness of ART treatments. It would be an appropriate organisation or scheme to review this information.

**Haplogroup matching**

5.62 Chapter three discussed the ongoing scientific debates around the need for haplogroup matching. This chapter highlighted that while there was still disagreement in the scientific community regarding the potential level of risk involved in 'mixing' haplogroups, there was consensus that any risk was far lower than the known risks of passing on mitochondrial disease.

5.63 Professor Thorburn submitted he is concerned that requiring haplogroup matching would reduce the pool of possible donor eggs and that:

Until there is more experience with mitochondrial donation, it seems reasonable to recommend haplogroup matching if practicable but to enable couples to choose to use an unmatched haplogroup donor.

5.64 Leaving the decision to about whether to use haplogroup matching, after counselling, to the prospective parents was endorsed by the Australian Academy of Sciences, Murdoch Children's Research Institute and Victorian Genetic Clinical Services and Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska.

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54 Mandatory reporting of any adverse events is required, such as birth defects, genetic abnormality or another adverse outcome such as a miscarriage.


56 Scientists in Reproductive Technology (SIRT) is a sub-committee of the Fertility Society, consisting of embryologists and other scientists involved in ART.

57 Dr Nadine Richings, Vice Chair, SIRT, *Committee Hansard*, 17 May 2018, p. 42.

58 Murdoch Children's Research Institute, *Submission 23*, p. 6.

Embryo sex selection

5.65 Many submitters and witnesses discussed the proposal in the United States that mitochondrial donation would be limited to only use male embryos, so that any negative germline modifications would not be passed on to subsequent generations. The Australian Academy of Science submitted that this was considered by the HFEA for mitochondrial donation in the UK, but was ultimately rejected due to concerns this would require another intervention, in this case PGD, in an embryo that had already been subject to heavy manipulation, and would also halve the number of suitable embryos and reduce the chance of achieving a pregnancy.60

5.66 The NHMRC ethical guidelines for ART allows for sex selection of embryos to reduce the risk of transmission of a genetic condition, disease or abnormality, but not for family balancing or other reasons.61 Whether or not the selection of male embryos to reduce the chance of passing on inheritable changes brought about by mitochondrial donation would be considered under these guidelines as an acceptable option, would have to be explored by the NHMRC. The choice for undertaking sex selection would then lie with the parents.

5.67 Professor Sue noted that this would also require careful pre-treatment counselling from a qualified geneticist:

[F]or patients who are dealing with a choice of having a male child with a maternity-transmitted disorder that may be something of importance and something that you or I are not able to inflict or control from any individual's choice. If the procedure is such that mitochondrial donation does or does not enable the choice of a male child, that is something I would have to guide the patient on: 'These are the risks. If you have the mitochondrial donation the risk is low. However, if they are a female they have a likelihood of passing it on if there is still some carryover'…That's something that a reproductive options clinic would offer and something that we would intend to do and evaluate after the procedure would be legalised.62

Pre-treatment counselling

5.68 The need for pre-treatment counselling was raised by multiple submitters, to ensure that couples considering using mitochondrial donation were fully informed of the known and unknown risks, the efficacy of the treatment, as well as other options for having genetically or non-genetically related children.63

60 Australian Academy of Science, Submission 35, p. 5.
61 NHMRC, Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research, para 8.1.
63 See for example: AMDF, Submission 26.1, [p. 6]; Australian Academy of Science, Submission 35, p. 5; Fertility Society, Submission 27, p. 2; Human Genetics Society of Australasia, Submission 2, p. 2; Murdoch Children's Research Institute, Submission 23, p. 2; Dr Shanti Balasubramaniam, Submission 52, [p. 5]; Associate Professor Newson, Submission 29, p. 3.
The AMDF submitted that the UK model offers a good basis for pre-treatment counselling and closely aligns with Australian pre-treatment counselling for ART procedures. AMDF further submitted that:

In terms of counselling, it seems appropriate that advice should be provided to prospective parents about the alternative options available to them in terms of their reproductive options and about the scientific concepts involved, such as pronuclear transfer, maternal spindle transfer, and potential haplogroup matching. In addition, in line with current medical practice regarding IVF, the risks and benefits of the procedures should be outlined.\(^{64}\)

Professor Thorburn also stressed the range of information that should be provided to parents in order to facilitate informed consent.

Parents need to know what the full range of options is, including adoption, egg donation, prenatal diagnosis, preimplantation genetic diagnosis and mitochondrial donation. Some of those options either will not be suitable for the families or will not be acceptable to the families, but it’s important that they be provided with all the information about potential safety and efficacy.\(^{65}\)

**Committee view**

The committee concurs with the views of the majority of submitters and witnesses, that the UK model of regulation provides a sound basis for adaptation to the Australian ART clinical context. The evidence shows that Australian clinics have the capacity to refine the skills necessary to undertake mitochondrial donation. Evidence also shows that the Australian research and clinical practice frameworks are sound and robust enough to be adapted to ensure that mitochondrial donation is regulated and appropriately monitored.

The committee notes that evidence presented to this inquiry on the areas of oversight for an appropriate regulatory regime will be useful to establishing an appropriate Australian system for mitochondrial donation.

The committee stresses the importance of detailed pre-treatment counselling for anyone who seeks mitochondrial donation as a treatment, to ensure they are fully aware of the risks, efficacy and other options that may be available to them.

**Accessing overseas clinics**

Professor Sue explained to the committee that her mitochondrial disease clinic has been in discussions with the fertility clinic in the UK which holds the licence to provide mitochondrial donation:

Through our planned Reproductive Options Clinic, Australian women with MD will be provided with a pathway by which they can undergo mitochondrial donation under safe and regulated conditions at the

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\(^{64}\) AMDF, *Submission 26.1*, [p. 9].

\(^{65}\) Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 15.
Mitochondrial Donation Centre in Newcastle, UK. However, this avenue, while helpful for some women, will be prohibitively expensive for others.\(^{66}\)

5.75 However, Professor Sue also outlined that other countries such as Mexico and Vietnam are offering this technology as 'medical tourism', without adequate regulations or academic oversight. Professor Sue argues that allowing mitochondrial donation in Australia will 'provide Australians with the opportunity to undergo procedures that are quality controlled, approved and regulated'.\(^{67}\) A number of other submissions also raised this as a significant concern and that Australian mitochondrial disease support groups have already been contacted by a clinic in Vietnam offering these services to Australians.\(^ {68}\)

5.76 Whether Australian legislative prohibitions on mitochondrial donation would make such actions an offence for an Australian couple has not yet been tested.\(^ {69}\)

5.77 To address the issue of Australians accessing treatment overseas, submitters recommended consideration of modifying Australian law to allow for this. Dr Newson further recommended there should be post-birth arrangement in place in Australia for any couples who successfully sought treatment overseas.\(^ {70}\)

**Committee view**

5.78 The committee understands that although the UK clinic offering mitochondrial donation is not yet accepting Australian patients, this may occur before this treatment is available in Australia. The committee also notes that mitochondrial donation may become available in less well-regulated countries. Any consideration of changes to legislation should take these issues into account.

**State law**

5.79 Many submitters pointed out that Victoria, New South Wales, South Australia and Western Australia have state-based legislation around reproductive technology, which would also have to be amended to allow for mitochondrial donation.\(^ {71}\)

5.80 For example, under state reproductive health laws, all Australian jurisdictions require the genetic origins of the resulting child be certain. In some states, this would constrain the implantation of more than one embryo where mitochondrial donation has

\(^{66}\) Professor Sue, *Submission 24*, p.5.

\(^{67}\) Professor Sue, *Submission 24*, p.5.


\(^{69}\) Distinguished Professors Jenni Millbank and Isabel Karpin and Professor Anita Stuhmcke, *Submission 57*, p. 5.

\(^{70}\) Associate Professor Newson, *Submission 29*, p. 6. This was also recommended by the Human Genetics Society of Australasia.

\(^{71}\) NHMRC, *Submission 4*, p. 1. See also Associate Professor Newson, *Submission 29*, p. 7; Australian Academy of Science, *Submission 35*, p. 7.
been used, and may also preclude anonymous mtDNA donation.\(^\text{72}\) In other states, such as NSW, Commonwealth anti-cloning laws have been replicated and would require amendment to allow for mitochondrial donation to be undertaken in that jurisdiction.\(^\text{73}\)

5.81 State-based laws do provide some regulatory opportunities, in that some states have regulatory bodies which could incorporate a role in overseeing mitochondrial donation, such as the Victorian Assisted Reproductive Treatment Authority. The Murdoch Children's Research Institute, however, argued that a national approach to regulation would be preferred.\(^\text{74}\)

**Committee view**

5.82 The committee understands that reproductive technology is regulated at both a Commonwealth and state level. In some cases, states have replicated Commonwealth anti-cloning laws. In order for mitochondrial donation to be used in clinical practice, this will require some amendment to the state or territory laws of the jurisdiction where the initial clinic(s) are established. This will best be addressed by the relevant Health Ministers working collaboratively, potentially through a Council of Australian Governments process.

**Public consultation**

5.83 Given the ethical considerations of mitochondrial donation, many submitters and witnesses acknowledged that public consultation should occur prior to changes in the legislation and any rollout of the clinical use of mitochondrial donation. Professor Christodoulou noted that this is an area where the views of the whole community should be taken into account, not just those with a specific interest in this treatment.\(^\text{75}\)

5.84 AMDF noted that this inquiry itself was part of the process to review the science and the ethics and gauge public opinion.\(^\text{76}\)

> I believe that most Australians provided with the relevant information would support the use of mitochondrial donation to prevent the devastating outcomes of mitochondrial disease.\(^\text{77}\)

5.85 Many submitters stressed the importance of accurate information being provided to the public during any consultation, and avoiding emotive and incorrect terms such as 'three-parent babies'.\(^\text{78}\)

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\(^\text{72}\) Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, p. 6.
\(^\text{74}\) Murdoch Children's Research Institute, *Submission 23*, p. 13.
\(^\text{75}\) Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 14.
\(^\text{76}\) Mr Sean Murray, Chief Executive Officer, AMDF, *Committee Hansard*, 17 May 2018, p. 9.
\(^\text{77}\) Murdoch Children's Research Institute, *Submission 23*, p. 13.
\(^\text{78}\) Human Genetics Society of Australasia, *Submission 2*, p. 4. See also: Australian Academy of Science, *Submission 35*, pp. 4, 8; Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 5]; Associate Professor Newson, *Submission 29*, p. 4.
5.86 Associate Professor Mills also stressed the importance of maintaining 'transparency and accuracy in discussions about the therapeutic efficacy of mitochondrial donation'. Associate Professor Mills told the committee:

Mitochondrial diseases can be caused by mutations in nuclear DNA that control mitochondria as well as mitochondrial DNA. This technology only addresses mitochondrial disease that arises from mitochondrial DNA, which is inherited maternally. Given this, it's important in discussions of mitochondrial donation that its capacity to cure or treat mitochondrial disease is not overstated. It's not a cure for existing people but a means of preventing the birth of some people who are likely to be born with mitochondrial disease—or, to put the point more positively, enabling the birth of people without such diseases.79

5.87 Dr Newson discussed a citizens' jury she recently conducted into community attitudes on mitochondrial donation. Dr Newson submitted that '[i]f citizens are provided with good quality evidence and have the opportunity to reason and think on the question at hand, they will be able to come to a well-informed and soundly reasoned decision that reflects their values'. Dr Newson outlined the process where participants 'hear balanced evidence, [from expert witnesses] have the opportunity to ask the experts questions, deliberate (with and without a neutral facilitator present) and come to a decision – the "verdict", which can include dissenting opinions'. The jury ran over one and a half days and comprised 14 members from a range of ages and cultures, who had no experience of mitochondrial disease.80

5.88 Dr Newson submitted that while the report of the citizen's jury has not yet been published, she did note that a 11 of 14 jurors answered either 'yes' or 'yes with conditions' (such as an appropriate licensing regime) to the question of whether Australia should allow children to be born following mitochondrial donation.81

5.89 Associate Professor Mills summed up the need for public consultation to take place in Australia around mitochondrial donation:

Furthermore, while we can learn from the UK process that took place in the lead-up to legislative reform, that process of public discussion can't simply replace a similar process in Australia. The issues involved in mitochondrial donation are sufficiently complex, and the potential regulatory reform sufficiently far-reaching, that a robust process of public and expert consultation and debate is required prior to its introduction into clinical practice.82

79  Associate Professor Mills, Committee Hansard, 17 May 2018, p. 51.
80  Associate Professor Newson, Submission 29, p. 7.
81  Associate Professor Newson, Submission 29, p. 8. Citizen's jury outcomes quoted from 'Using deliberative engagement to assess public attitudes towards novel reproductive technologies: a citizens' jury on mitochondrial donation': Confidential attachment to Submission 29; cited with permission.
82  Associate Professor Mills, Committee Hansard, 17 May 2018, p. 52.
Committee view

5.90 The committee agrees that mitochondrial donation should not be introduced without allowing for public consultation.

5.91 The committee notes that this inquiry plays a part in public consultation, and considers that from the evidence presented so far, mitochondrial donation may not be seen as a controversial medical treatment.

5.92 The committee further notes that any legislative change will, most likely, involve a Senate legislation inquiry, which will give further opportunity for the Australian public to put their views to the parliament on whether this treatment should be legalised.

5.93 The committee agrees that public consultation is necessary before any full rollout of mitochondrial donation and that parliamentary inquiries alone will not be sufficient public consultation.

5.94 Evidence suggests that mitochondrial donation is a form of genetic modification that was not envisioned at the time that anti-cloning laws were enacted in Australia. As such, these laws prevent mitochondrial donation from being researched and used in clinical practice. Science has moved significantly faster than legislation.

5.95 Therefore, as outlined in chapter four, a foundational question must be answered before any possible introduction of mitochondrial donation into Australian clinical practice: does this treatment constitute germline gene modification in the manner known at the time that such practices were prohibited under Australian anti-cloning laws, and is it appropriate to modify laws to incorporate mitochondrial donation?

5.96 Defining what kind of gene modification this treatment is, is fundamental to developing the most appropriate legislative amendments to legalise mitochondrial donation if that is supported by the community. The committee does not envision this process as requiring an extensive or lengthy review.

5.97 The committee concurs with the views of many submitters and witnesses, that, should mitochondrial donation be introduced to Australia, enacting a regulatory and oversight regime for mitochondrial donation would be most appropriately done through regulations which empower the NHMRC, supported by the RTAC of the Fertility Society to manage the oversight and restricted access to mitochondrial donation as a clinical treatment.

5.98 In this way, regulations can be amended and adapted to keep up to date with changing scientific knowledge, with the review and approval of the Parliament of Australia.
Recommendations

Recommendation 1

5.99 The committee notes the strong potential of mitochondrial donation to address the debilitating effects of inheriting mitochondrial disease. The committee recommends that public consultation be undertaken regarding the introduction of mitochondrial donation to Australian clinical practice. To facilitate this consultation, the committee further recommends the Australian Government prepare a consultation paper, including options for legislative change that would be required. The Minister for Health should seek advice from the National Health and Medical Research Council on the most appropriate timing and format for this consultation.

Recommendation 2

5.100 The committee recommends that the Australian Government task the National Health and Medical Research Council with advising on the following questions:

- Whether mitochondrial donation is distinct from germline genetic modification.
- Is there any new information to indicate that research findings from the United Kingdom, that the science of mitochondrial donation is safe for introduction into controlled clinical practice, cannot be applied in an Australian context?
- Whether other approaches to inheriting mitochondrial disease should also be the focus of Australian research.

5.101 The committee recommends the findings be used to inform future legislative process.

5.102 The committee notes that the Prohibition of Human Cloning for Reproduction Act 2002 and the Research Involving Human Embryos Act 2002 would require amendment to insert a power to make regulations allowing for mitochondrial donation, with an appropriate regulatory regime overseen by the National Health and Medical Research Council.

Recommendation 3

5.103 The committee recommends the Minister for Health take the findings of this report to the Council of Australian Governments (COAG) Health Council to progress the implementation of this report's recommendations with the states and territories.
Recommendation 4

5.104 The committee recommends, noting the need for community consultation and scientific review, the urgency of treatment for current patients and the small number of patients seeking this treatment, that the Australian Government initiate dialogue with the relevant authorities in the United Kingdom to facilitate access for Australian patients to the United Kingdom treatment facility as an interim measure.

Senator Rachel Siewert
Chair