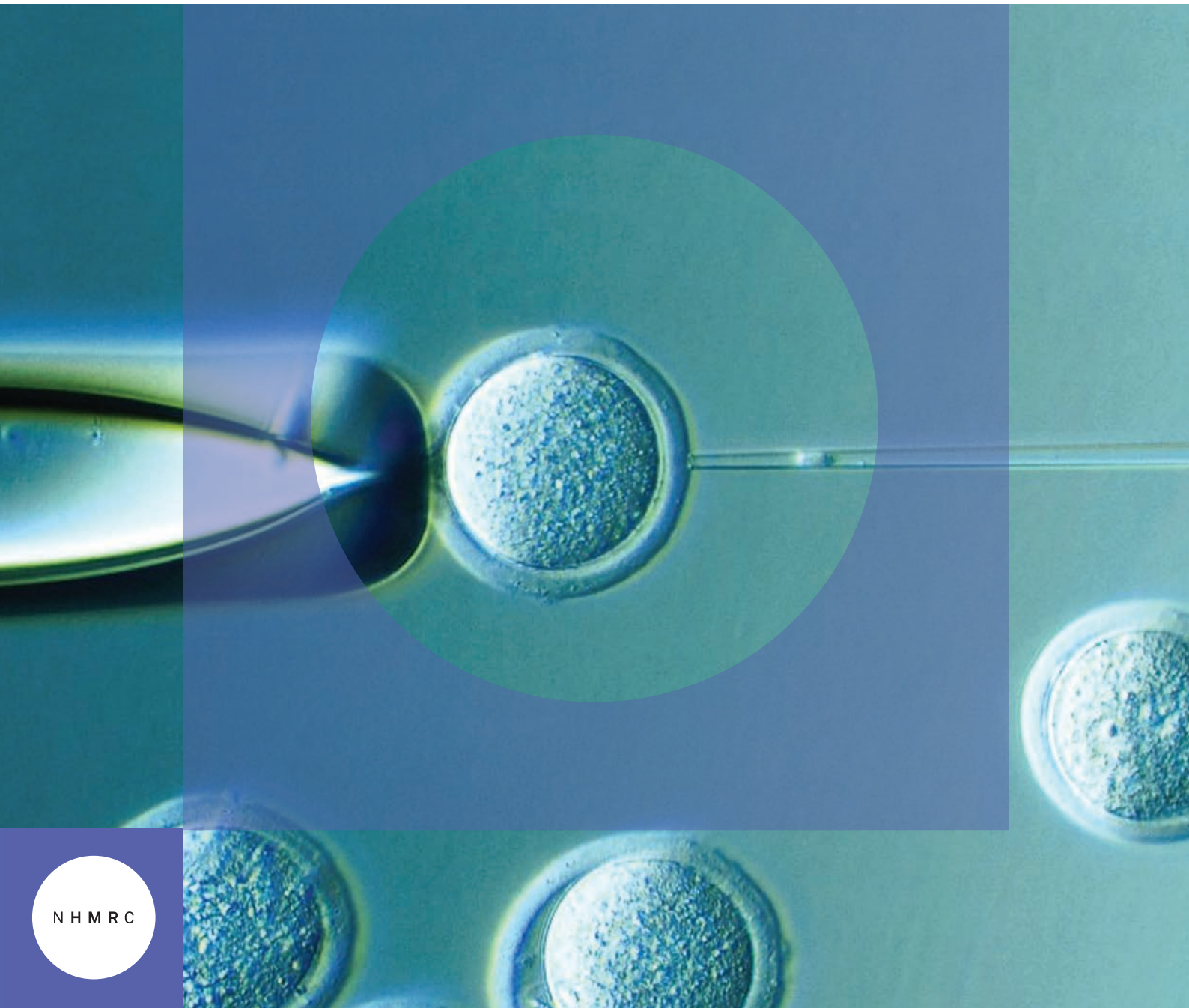
Australian Government
National Health and Medical Research Council

BUILDING
A HEALTHY
AUSTRALIA

Mitochondrial Donation Issues Paper

Ethical and Social Issues for Community Consultation



NHMRC

Australian Government

National Health and Medical Research Council

Have your say by visiting
www.nhmrc.gov.au/mito

Online submissions are open from
23 September to 29 November 2019.

NHMRC

Purpose of this Paper

Mitochondrial DNA disease is an inherited condition that can cause serious health issues and, in severe cases, reduced life expectancy. Mitochondrial donation is a new assisted reproductive technology to help people avoid transmitting mitochondrial DNA disease to their biological children. Applied in conjunction with IVF, it is in limited use in the UK and some other countries, but not Australia. Mitochondrial donation might be able to assist in the prevention of mitochondrial DNA disease in an estimated 60 births per year in this country. NHMRC is asking the Australian community to consider the social and ethical issues associated with mitochondrial donation.

This paper provides an overview of mitochondrial donation and related ethical and social issues in the context of Australian law. The purpose of this paper is to inform and engage the Australian community and to seek views on the issues raised. This paper outlines:

- what mitochondrial disease is and who it affects
- how the technology of mitochondrial donation works
- how current Australian law limits the application of mitochondrial donation
- ethical and social considerations around this technology
- a glossary of key terms.

Overall, this consultation process aims to understand whether an informed community, having considered the issues, would support the introduction of mitochondrial donation into Australian clinical practice at this time.

Who is the Target Audience for this Paper?

This paper is for a general audience and in-depth scientific knowledge is not required. It seeks to capture the complexity of the issues associated with mitochondrial donation in an accessible way. All respectful contributions to this consultation process from the Australian community are encouraged, including those from individuals or on behalf of groups or organisations.

Limitations of Scope

The primary focus of the public consultation is on the ethical and social issues associated with mitochondrial donation as a new assisted reproductive technology to help people avoid transmitting mitochondrial DNA disease to their biological children.

The following issues are not being considered through this consultation:

- uses of mitochondrial donation other than for preventing transmission of mitochondrial DNA disease
- other forms of assisted reproductive technology, including those that are already in clinical use
- treatments for people already living with mitochondrial disease.

NHMRC

Executive Summary

This issues paper presents some scientific background plus social and ethical considerations around the application of mitochondrial donation as a technology to prevent the transmission of mitochondrial DNA disease from a parent to their biological children. It invites contributions from the Australian community.

Mitochondrial DNA disease is debilitating and currently incurable. It includes a broad group of health conditions resulting in physical disabilities, metabolic problems, abnormal organ function and early death for some patients. Signs and symptoms are incredibly varied.

Between one in 5,000 and one in 10,000 Australians are estimated to develop severe mitochondrial DNA disease during their lifetime. The average lifespan of children with mitochondrial DNA disease is estimated to be between three and 12 years of age. More people still develop mitochondrial disease as adults.

The symptoms of mitochondrial DNA disease result from mutated mitochondrial DNA being passed from mother to child in small structures inside the egg called mitochondria.

More than 99.9% of our genes come from both our parents, carried in nuclear DNA. The remaining genes come from mitochondria in our mother's egg. These genes are critical to the normal functioning of human cells.

A technology known as **mitochondrial donation** could lower the risk of some women passing on mitochondrial DNA disease to their children. Put simply, it involves replacing mitochondrial DNA from the mother with healthy mitochondrial DNA from the egg of another woman, an egg donor.

Mitochondrial donation may represent the only option for some parents to have a genetically related child without mitochondrial DNA disease.

Mitochondrial donation for reproductive purposes is currently prohibited in Australia. It is in limited use in the UK and some other countries.

A lot remains unknown about the technology. From a scientific perspective, immediate and long-term risks for the child are still yet to be fully understood. Longer term implications for subsequent generations also remain unknown.

In addition to scientific considerations, the Australian community is likely to hold a range of views regarding ethical and social issues for mitochondrial donation as a clinically available assisted reproductive technology.

This issues paper provides an overview of mitochondrial donation and the related ethical and social issues. The purpose of this paper is to inform and engage the Australian community and to seek views on the issues raised.

The paper presents an overview of mitochondrial don ation, presented under the following headings:

- Mitochondria in cells contain DNA that is vital for good health
- What is mitochondrial DNA disease?
- How mitochondrial donation technology works
- We still don't know everything about mitochondrial donation
- Where mitochondrial donation fits with Australian law

The paper then presents a summary of ethical and social considerations of mitochondrial donation, addressing:

- The rights of the child, future adult and future generations
- The status of the embryo
- Donor roles and interests
- Community considerations

Questions for public consultation and a glossary are also included.

Mitochondria generate the energy that our cells need to function.

Overview of Mitochondrial Donation

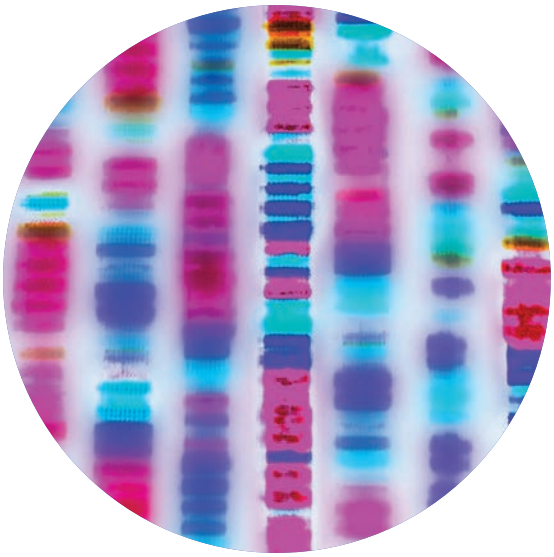
Mitochondria in cells contain DNA that is vital for good health

As individual humans, each of us inherits the vast majority of our genes from both our mother and father. These genes come from the nucleus of our parents' egg and sperm cells. But we also inherit about 37 additional genes from our mother only. These genes came from thousands of microscopic cell structures called mitochondria in our mother's egg. Mitochondria are essential to the working of human cells.

There are several key differences between nuclear DNA and mitochondrial DNA.

- Nuclear DNA is inherited from both biological parents, but mitochondrial DNA is inherited from the biological mother.
- Mitochondrial DNA contains 37 genes, compared to the 20,000–30,000 genes found in nuclear DNA. The roles of mitochondria and mitochondrial DNA are described in Box 1. Nuclear genes are essential for nearly all cellular processes and code for personal characteristics such as hair and eye colour.
- Nuclear DNA is assembled in chromosomes contained in the nucleus of the cell. There are usually 46 chromosomes (two copies of each of the 23 chromosomes) in the nucleus of most cells in the human body. There is usually just one nucleus per cell.
- In contrast, the amount of mitochondrial DNA can vary greatly from mitochondrion to mitochondrion, as well as from cell to cell. For example, some cells may have fewer than 20 copies of mitochondrial DNA, while human eggs have up to 500,000 copies (Figure 1).

Nuclear and mitochondrial DNA are located in different structures and have unique roles in cells. A consideration of the social and ethical implications of technologies that target mitochondrial DNA can be considered separately from emerging technologies that target nuclear DNA.



A read out of a DNA sequence.
Image © Gio_tto, istock

The mitochondrial network defines the outline of this cell. DNA is red, with a vibrant nucleus and little outposts of mitochondrial DNA in the network.
Image © Odra Noel, Wellcome Images

Figure 1.

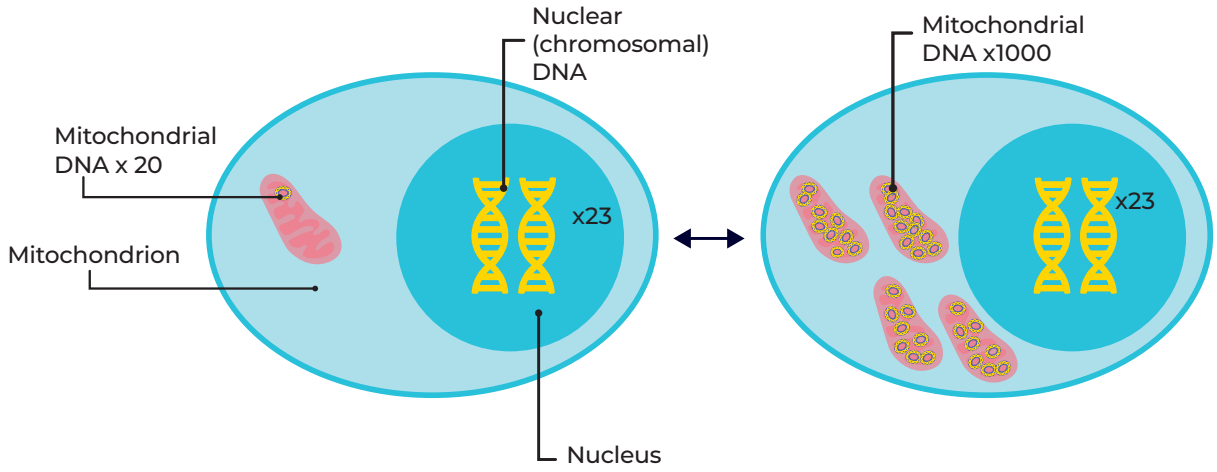


Figure 1. The numbers of mitochondria (pink) in each cell and mitochondrial DNA (yellow circles) in each mitochondrion vary greatly; however, most cells have a single nucleus (dark blue) with DNA in the form of 23 pairs of chromosomes (yellow). In a given cell there are at most two copies of each of the nuclear genes, whereas there could be tens to tens of thousands of copies of each of the mitochondrial genes. Diagram is not to scale.

Box 1.

What are mitochondria?

Mitochondria are DNA-containing structures found in human cells. Although small, mitochondria are vital for normal cell biology and health.

They provide energy for cells, and support many other important functions.

Mitochondria are involved in:

- determining people's susceptibility to certain diseases
- reproduction
- cancer and inflammatory responses
- normal cell functioning and turnover
- regulation of metabolism, and
- ageing.

Mitochondrial DNA and nuclear DNA work together in cells. For example, mitochondria regulate how nuclear DNA is expressed to become proteins. The opposite also applies: more than 1,000 nuclear genes relate to mitochondrial function.

Mutations in mitochondrial DNA can result in mitochondrial disease, which can be severe and life threatening. These mutations can be passed from mother to child.

What is mitochondrial DNA disease?

Mitochondrial DNA disease refers to a group of conditions where inherited abnormal mitochondrial DNA can create health problems and lowered life expectancy. The disease can be fatal, and there is no known cure. One in 5,000 Australian babies is born with a severe or life threatening form of mitochondrial DNA disease. Approximately one in 200 people carry mitochondrial DNA mutations that could cause disease.

Mitochondrial DNA disease refers to a group of inherited conditions that can significantly lower a person's health and life expectancy, and may be fatal. Currently, there is no known cure, and treatment options are limited largely to management of symptoms.

This paper focuses on mitochondrial disease caused by mutations, or inherited abnormalities, in mitochondrial DNA. It should be noted that mutations in nuclear DNA can also cause mitochondrial disease.

The average lifespan of children with mitochondrial DNA disease is estimated to be between three and 12 years of age. However, mitochondrial DNA disease can affect people at any age – some individuals don't develop symptoms until their adult years.

Between one in 5,000 and one in 10,000 Australians are estimated to develop severe mitochondrial DNA disease during their lifetime. Almost all these individuals will have high amounts of mutated mitochondrial DNA in affected tissues and organs.

Many other Australians (approximately one in every 200 babies born) are born with some level of mutation in mitochondrial DNA that could lead to mitochondrial DNA disease. However, it appears that many of these individuals have levels of mutated DNA too low to cause disease.

Due to the role of mitochondria in energy production, mitochondrial disease particularly affects organs that use the most energy, such as the heart, muscles and brain. But the symptoms and prognosis for people with mitochondrial DNA disease depend on the type and number of mutations, and how the affected mitochondria are distributed among tissues and organs.

Severe changes in mitochondrial DNA can cause life-threatening mitochondrial DNA diseases, while milder changes present in the population can influence metabolic responses and may influence susceptibility to common diseases. Symptoms range from fatigue to diabetes, deafness, heart failure, liver failure, respiratory failure, strokes, seizures, intellectual disability and dementia.

Mitochondrial DNA disease can cause so many different symptoms because mitochondria are located everywhere within the body. Some mitochondrial disorders might only affect a single organ, but most involve multiple organs.

Many different health conditions can be described as mitochondrial DNA disease. However, many forms of mitochondrial DNA disease have not been named because the symptoms vary from patient to patient, so cannot be grouped together as a specific condition.

It's difficult to predict what impact mitochondrial DNA disease will have on each individual patient, and symptoms can change over time.

People with mitochondrial DNA disease may have a mix of healthy and mutant mitochondrial DNA in their cells, which may affect the severity of their disease.

A cell can have a mixture of healthy and mutated mitochondrial DNA. This is called heteroplasmy.

The proportion of unhealthy mitochondrial DNA (referred to as mutation load) may affect the severity of mitochondrial DNA disease (see Figure 2). Low levels and types of mutations may mean that a person does not exhibit any symptoms of mitochondrial DNA disease.

Figure 2.

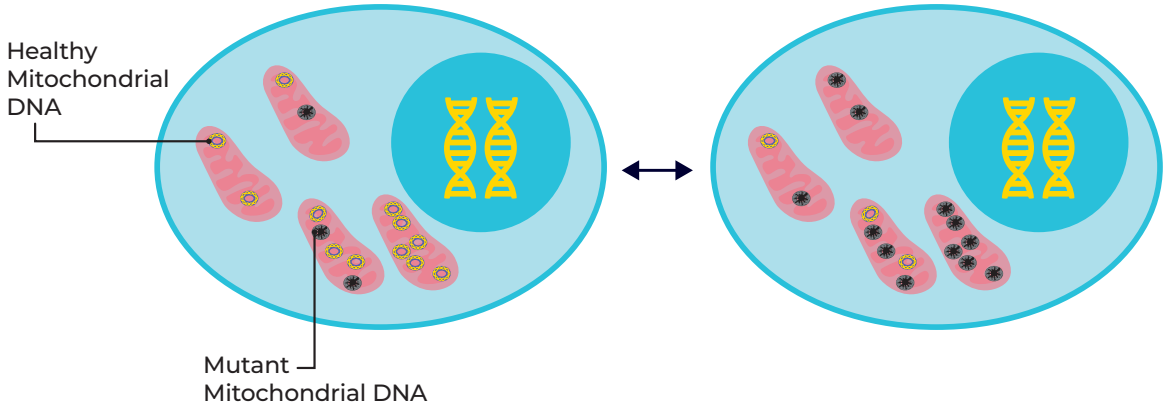


Figure 2. Mitochondrial DNA disease can range from being mild (left), where substantial numbers of mitochondria (pink) contain healthy mitochondrial DNA, to severe (right), where all, or nearly all, mitochondria contain severely mutated DNA (grey circles). Diagram is not to scale.

Levels of heteroplasmy may change over time and may vary between organs and tissues within the same person. Levels may also vary between individuals in the same family.

Transmission of mitochondrial DNA disease from a mother to her biological children is a complicated process. It can be difficult to know in advance the likelihood of a woman transmitting mitochondrial DNA disease.

Mitochondria for a future child will come from the egg, and not from the sperm. This means it's only mothers, not fathers, who pass on mitochondria to their children. Each egg contains thousands of mitochondria.

Women who are heteroplasmic carriers of mitochondrial DNA disease have a mix of normal and mutated mitochondrial DNA. As a result, it is difficult to know in advance whether they will pass on mitochondrial DNA disease to their biological children, or how severe it will be, or even when in a person's life symptoms will develop. Such women can produce eggs with a variety of mutation loads, from eggs with low levels of mutated mitochondrial DNA to those with 100% affected mitochondrial DNA. A higher mutation load in the egg is more likely to result in severe mitochondrial DNA disease in the baby.

Mitochondrial donation may represent the only option for some parents to have a genetically related child without mitochondrial DNA disease.

Having biological offspring who are genetically connected to both parents is highly desirable for many people. But these people face difficult choices when they know they are at risk of conceiving a child with mitochondrial DNA disease.

Some may choose not to have children at all.

Some people may decide to conceive naturally despite the chance of transmitting mitochondrial DNA disease. Following a natural conception, prenatal testing of fetal or placental tissues may be tried in an attempt to assess the risk of mitochondrial disease in the fetus (developing baby). However, this approach is not always straightforward, and is typically only suitable for couples where the woman has a low amount of mutated mitochondrial DNA.

What is mitochondrial DNA disease? (cont'd)

Assisted reproductive technologies present additional options for parents wanting to reduce the risk of transmitting mitochondrial DNA disease. Preimplantation genetic testing (PGT) can be used to select embryos with a lower risk of mitochondrial DNA disease following in vitro fertilisation (IVF). However, this technique is not appropriate for all women, especially those with a high mutation load. Also, it also does not always give an accurate indication of the risk of developing mitochondrial DNA disease.

Alternatively, parents may choose to conceive using an egg donated by another woman.

However, there are a number of barriers to using a donor egg for people with mitochondrial DNA disease (Box 2). For women with mitochondrial DNA disease, these barriers can be significant.

Some families may wish to explore the possibility of fostering or adopting children. However, such children are not usually genetically related to the parents. Furthermore, fostering or adoption can present limited options for Australians. For example, very few infants are relinquished for permanent adoption by Australian families. Further, adoption is subject to screening and assessment processes and parental age limits, which might preclude some prospective parents.

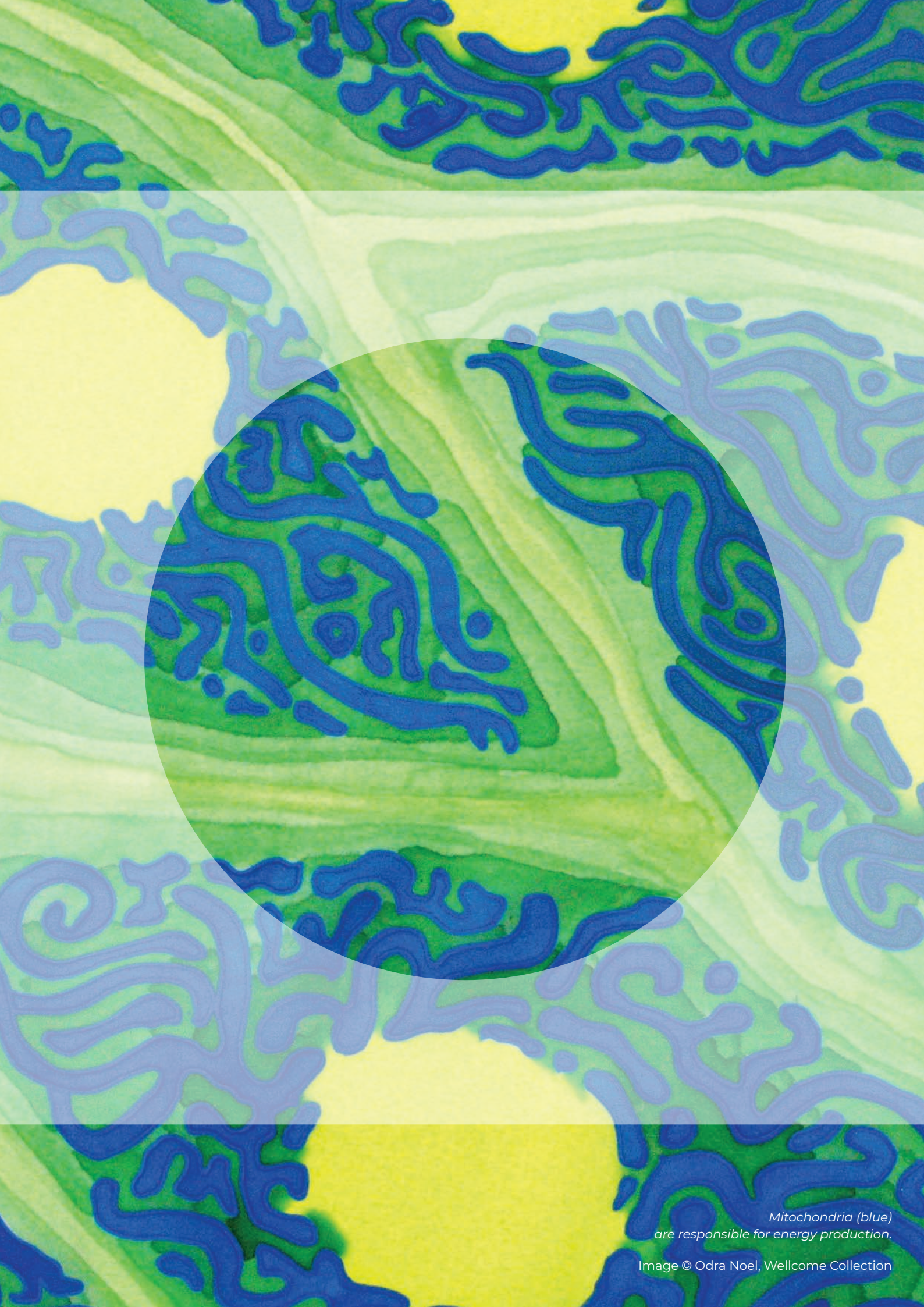
Given these factors, in some cases, a technology known as mitochondrial donation may represent the only option for parents to have a genetically related child without mitochondrial DNA disease.

Box 2.

Barriers to using a donor egg for people with mitochondrial DNA disease.

These include:

- there are a limited number of egg donors in Australia
- an egg donor should not be maternally related to the intending mother
- an egg donor must be tested for mitochondrial DNA disease
- the collection process can be demanding and unpleasant for the donor, and
- there is a low success rate of donor egg conceptions.



Mitochondria (blue)
are responsible for energy production.

How mitochondrial donation technology works

Mitochondrial donation allows for an embryo to be produced using the nuclear DNA from a man and a woman, and the mitochondrial DNA from an egg donated by another woman. There are a number of techniques for mitochondrial donation. The aim is to replace mutant mitochondrial DNA, and avoid transmission of mitochondrial DNA disease.

Mitochondrial donation aims to ensure that only healthy mitochondrial DNA is passed on to an embryo. The term collectively refers to techniques aimed at preventing the transmission of mitochondrial disease caused by mutations in mitochondrial DNA. It is also known as mitochondrial replacement therapy or mitochondrial transfer.

Mitochondrial donation cannot cure existing mitochondrial disease or prevent mitochondrial disease caused by mutations in nuclear DNA. However, it may be a way to prevent the transmission of mitochondrial DNA disease to offspring and potentially even future generations.

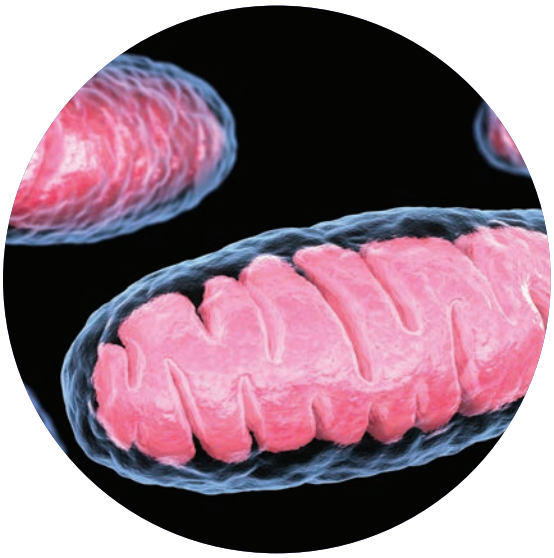
Mitochondrial donation might be able to assist in the prevention of mitochondrial DNA disease in an estimated 60 births per year in Australia.

Researchers are currently investigating a number of techniques for mitochondrial donation. These include maternal spindle transfer (MST), pronuclear transfer (PNT), polar body transfer (PBT) and germinal vesicle transfer (GVT), as shown in Figure 3.

All techniques result in an embryo with nuclear DNA from a man and a woman, and mitochondrial DNA from a separate woman, the egg donor. This requirement for egg donation has a number of barriers, as discussed in Box 2 on the previous page.

Mitochondrial donation is sometimes referred to in popular media as producing a “three-parent” baby. However, use of this and similar terminology has been criticised on numerous grounds by ethicists, clinicians and scientists and therefore is not used here.

In some techniques, an egg is reconstructed by replacing the donor’s nuclear DNA with the nuclear DNA from the mother. The reconstructed egg, which includes the egg donor’s mitochondria and the mother’s nuclear DNA, is fertilised with sperm from the father.



Mitochondria provide energy for cells and support many other important functions.
Image © iLexx, istock

In other techniques, eggs from the mother and egg donor are fertilised with sperm from the father to make two zygotes. A zygote is a fertilised egg at its earliest stage of development (that is, before the first cell division). The nuclear DNA from the zygote made from the donor’s egg is removed and discarded. It is then replaced with the nuclear DNA from the zygote produced from the mother’s egg.

Figure 3.

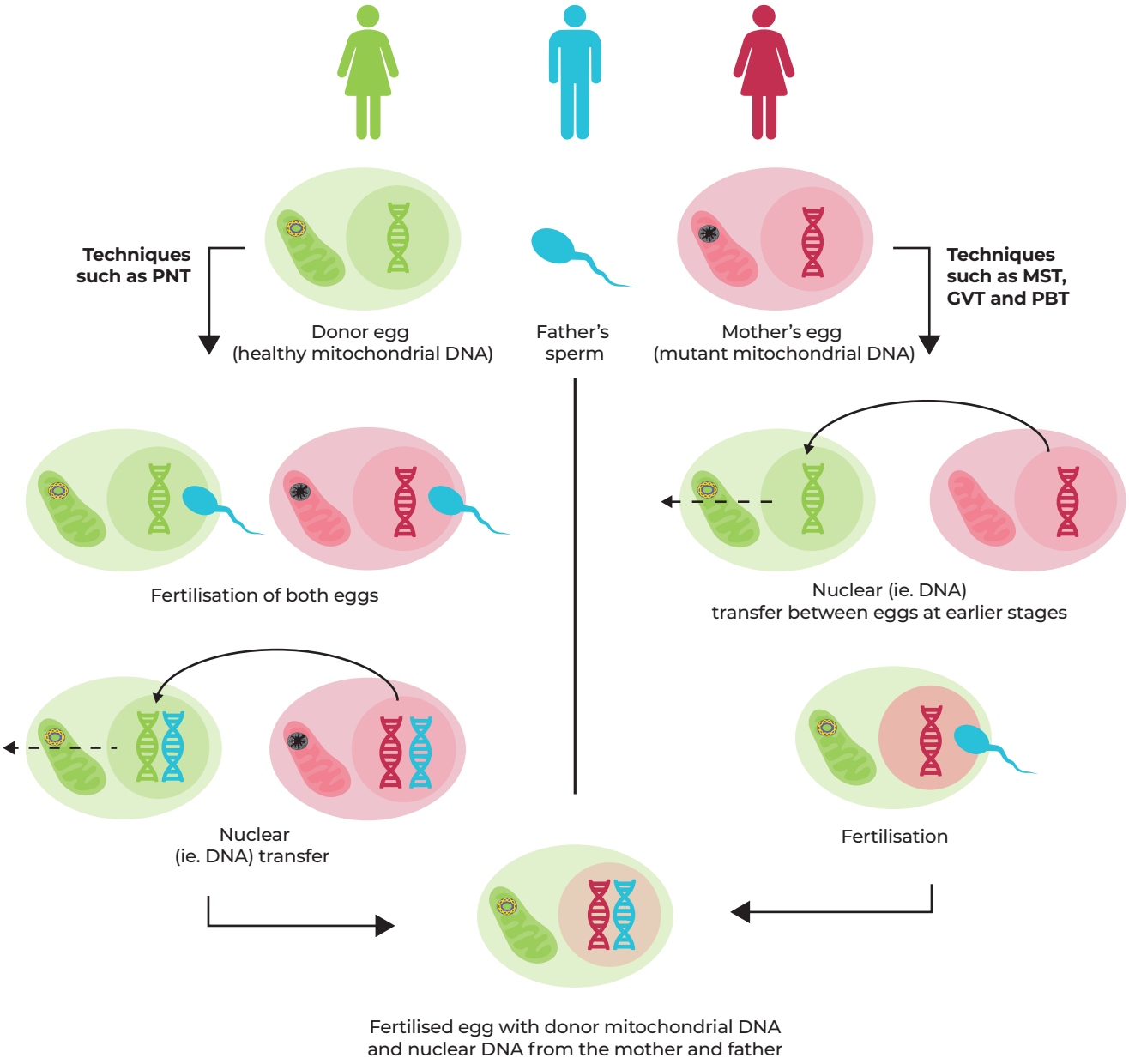


Figure 3. Simple depiction of techniques for mitochondrial donation. All techniques require a mother's egg (pink), father's sperm (blue) and a donor egg from another woman (green). The result is an embryo with nuclear DNA from the mother and father, and mitochondrial DNA from the egg donor. In some techniques such as pronuclear transfer (PNT), the nuclear DNA is transferred after fertilisation. In other techniques such as maternal spindle transfer (MST), germinal vesicle transfer (GVT) and polar body transfer (PBT), the nuclear DNA is transferred before fertilisation. Diagram is not to scale.

We still don't know everything about mitochondrial donation

The science of mitochondrial donation is complex and it is difficult to say with certainty whether this technology is safe and effective. Some risks of mitochondrial donation remain unknown. Community debate will help determine the level of risk individuals and the community are prepared to accept to use this new technology.

The risks associated with mitochondrial donation, as with other new medical technologies, are not yet completely understood.

Some scientists and clinicians consider there are some important questions relevant to the safety and effectiveness of mitochondrial donation that still need further research (see Box 3).

It could be possible to introduce mitochondrial donation technology in Australia under a research protocol and for training purposes, before any widespread introduction into clinical practice in IVF clinics. This research would initially involve producing embryos using mitochondrial donation and studying their development in culture to the blastocyst stage. A blastocyst refers to a five to seven day old embryo, composed of approximately 150 cells.

Mitochondrial donation introduces changes to human genomes that could be inherited by future generations.

The term 'heritable changes' refers to changes in DNA that can be inherited by future generations. While in the case of mitochondrial donation creating heritable changes in DNA could bring significant benefits in the prevention of disability or disease, significant ethical concerns are also relevant. These concerns may relate to the future unknown impact of heritable changes, the inability for future generations to give consent to these changes, the implications of changing a person's genetic makeup, and the potential use of the technology in ways that cause harm or are unacceptable to the community.

If mitochondrial donation results in a female child, when she reaches adulthood any of her offspring will also receive the egg donor's mitochondrial DNA. That is, a girl born following mitochondrial donation will have a different mitochondrial genome to her mother, and one that may be inherited by her own children.

Some consider it would be necessary to limit mitochondrial donation to the production of male embryos, at least initially, to prevent the donated mitochondrial genes from being inherited by future generations. However, this would reduce the efficiency of the intervention, as only around 50% of embryos would be accepted. Also, it would require an extra step of another invasive test to determine the sex of the embryo, which may raise its own safety and ethical concerns.

Alternatively, allowing female children to be born could be contingent on adequate follow-up initially of male children and satisfactory findings on the intergenerational effects from animal studies.

In the UK, a review of the science recommended mitochondrial donation technology is 'safe enough', which led to the UK government legalising mitochondrial donation under strict regulations.

In February 2015, the UK introduced legal regulations to allow the use of mitochondrial donation. This followed several reviews of the science and a public consultation on the social and ethical issues. While the practice is allowed, it is strictly regulated: access to the treatment is only approved on a case-by-case basis and only for patients at high risk of transmitting mutations that will lead to serious mitochondrial DNA disease.

Other countries, such as the USA, have not yet allowed the technique. Mitochondrial donation is also currently prohibited in Canada, but is reported to have been used in Mexico and the Ukraine, where its regulatory status is less clear.

Inconsistency in regulation globally could lead to medical tourism, where Australian couples travel overseas to access this technique. If the couple travels to a country where this technology is not well regulated, additional risks could arise.

Box 3.

Scientists are working to learn more about mitochondrial donation.

Some questions that are the focus of current research include:

1. **How much mutant mitochondrial DNA is transferred from the mother's affected eggs during the process of mitochondrial donation?**

   Several research studies have shown some carry-over of mitochondria from the woman with mitochondrial DNA disease into the reconstructed embryo. It is not yet known what level of carry-over may lead to a risk of mitochondrial DNA disease in the future child.

2. **How is the mutant mitochondrial DNA distributed as cells replicate and divide after fertilisation?**

   Some studies suggest the carried-over mitochondrial DNA can replicate more successfully than donor mitochondrial DNA. Consequently, a child born following mitochondrial donation could develop mitochondrial DNA disease during their life. Setting a threshold for carry-over (e.g. less than 2%) could minimise risk. However, the studies leading to these results were done in an unusual type of cell called embryonic stem cells, and experts disagree about clinical significance.

3. **Does mitochondrial donation result in significant changes to the development of the embryo, compared with normal embryo development?**

   Some experts are currently investigating whether the nucleus that is transferred from the mother's egg has to adapt to the new environment of the donor's egg, and if this affects the potential of the reconstructed egg to develop normally.

4. **Is compatibility between the nuclear and mitochondrial DNA important?**

   A study in mice with the same nuclear genome and different 'types' of mitochondrial DNA indicated that mismatched mitochondrial DNA may have detrimental long-term effects on the metabolism, health and longevity of animals. There is debate about the likelihood and extent of these findings being relevant to humans but, if they are, then the consequences could be significant. At the very least, it suggests the selection of a donor with compatible mitochondrial DNA could be important.

Where mitochondrial donation fits with Australian law

It may be possible to conduct some types of laboratory-based research into mitochondrial donation under licence in Australia. Clinical use of mitochondrial donation for reproductive purposes is currently prohibited in Australia.

In Australia, two Commonwealth laws regulate the use of human embryos in research and ban certain practices relating to the reproductive use of human embryos:

- *the Prohibition of Human Cloning for Reproduction Act 2002*, which prohibits certain practices in human reproduction and the use of human embryos
- the *Research Involving Human Embryos Act 2002*, which regulates scientific or research activities involving the use of certain human embryos created by assisted reproductive technology or by other means.

These Acts are also 'mirrored' by relevant legislation in most Australian states and territories.

Under these laws, some laboratory-based research into mitochondrial donation may be permissible in Australia under licence. Mitochondrial donation for reproductive purposes is currently prohibited in Australia.

The practice of assisted reproductive technology is guided by the Fertility Society of Australia Reproductive Technology Accreditation Committee's *Code of Practice for Assisted Reproductive Technology Units*. Compliance with the Code is mandatory for any units involved in the treatment of patients using assisted reproductive technology.

Some Australian states also have legislation specifically regulating the clinical practice of assisted reproductive technology.

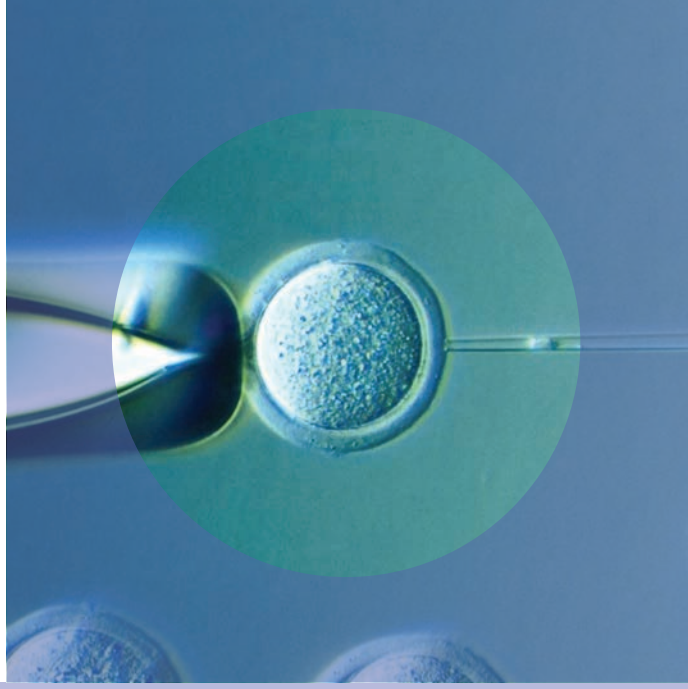
Amending the legislation to allow mitochondrial donation without also allowing other currently prohibited activities would be challenging.

Mitochondrial donation is a highly specialised technology. If it becomes legalised, expertise would likely be centralised in a limited number of Australian clinics, and could be conducted initially as part of a formal research study.

Mitochondrial donation techniques require manual dexterity and skill in the micromanipulation of eggs and embryos.

Training in mitochondrial donation techniques would involve the production of reconstructed embryos and a limited period of embryo culture to assess the success of the procedure. These embryos would then be discarded, as they would be prohibited from being transferred to a woman. This is consistent with the current accepted practice for research into assisted reproductive technologies that require the use of human embryos.

Ethical and social considerations of mitochondrial donation



In addition to questions around safety and effectiveness, scientists, researchers and others have identified ethical and social issues that arise from the use of mitochondrial donation in research and in clinical treatment. These include the rights of the child, the status of the embryo, the role and rights of women donating eggs, and community considerations. But these matters should also be subject to broader consultation. This section outlines the questions for the Australian community and invites your views.

The rights of the child, future adult and future generations

The interests and wellbeing of the people who may be born as a result of using mitochondrial donation must be considered, as they cannot choose whether to be involved. This includes issues of their long-term health and consent to ongoing follow-up.

Respect for the interests and wellbeing of the person who may be born from mitochondrial donation is an important consideration. This includes possible issues associated with their long-term health as a result of the technology.

While the technology is intended to prevent the transmission of mutant mitochondrial DNA from the child's mother, some of the health risks associated with the technology are unknown.

Some may argue that the person would not exist without the desire of their parents to be parents, including their willingness to use the technology, and that it is in the person's best interests to be born. Nevertheless, using mitochondrial donation necessitates accepting some uncertainties for the person born due to the potential longterm, heritable changes to the person's genetic makeup.

Others might propose that the interests and wellbeing of the potential child preclude the use of mitochondrial donation, because there is too great a risk, or too many unknowns, as to whether the child will be born or remain healthy throughout their life.

Another view is that it's unethical to delay the introduction of mitochondrial donation to prevent mitochondrial DNA disease.

While competent adults can exercise a choice about their involvement in mitochondrial donation, all decisions are being made on behalf of the resulting child. There is no way to get their view on which risks are acceptable to them as an individual.

Biological and social relationships for the child born as a result of mitochondrial donation need to be considered. Would the child have an interest in knowing or forming a relationship with the mitochondrial DNA donor? Some argue that the contribution of mitochondrial DNA is not enough of a basis for a child to need to have access to information on the woman who was the egg donor. However, failing to acknowledge the interests of the donor-conceived offspring in other situations has been acknowledged as ethically naïve and harmful in some cases. It is too soon to tell how children born of mitochondrial donation will view the woman who donated an egg in the future.

We need information on the health and wellbeing of the person born, as well as future generations, to assess the safety and effectiveness of mitochondrial donation and to progress our understanding of the science. However, families involved may choose not to give consent to ongoing follow-up.

The experimental nature of mitochondrial donation makes ongoing follow-up important for ensuring that the medical and social consequences of mitochondrial donation can be assessed.

However, privacy for children and their families is likely to be a significant concern. Families are more likely to consent to follow-up if relationships of trust and sound communication are developed with the clinicians. This may also occur if families understand how follow-up benefits the person born following mitochondrial donation and their relatives, as well as wider society.

One view could be that mitochondrial donation should only be offered, at least initially, as part of a research study that requires the parents to

Between one in 5,000 and one in 10,000 Australians are estimated to develop severe mitochondrial DNA disease during their lifetime. **Image © ideabug, istock**

agree to ongoing follow-up of the child's health, preferably over the longer term. Perhaps future generations should also participate in follow-up, so the intergenerational effect of the technology can be assessed.

This could have the effect of 'medicalising' the child by making them an ongoing subject of medical study. There are also issues with potential coercion of consent to ongoing follow-up and with privacy for the families, especially where the number of couples accessing the technology is likely to be small.

Some have argued that the child, and their families, should have the right not to participate in any further medical studies, or that any data collected on the health and wellbeing of the child should not be made available to others to protect the privacy of the families involved. This includes not making it available to researchers and clinicians seeking to improve the safety of the technique.

The status of the embryo

Mitochondrial donation involves the use of human embryos, which are generally regarded as morally significant. The Australian community should consider whether mitochondrial donation raises distinct social or ethical issues for the status of the embryo.

The Australian community holds a range of views about the status attributed to a human embryo.

Some people see the same embryo as a living human entity in the earliest stage of development or a potential life; others view it merely as a group of cells. Some argue that the value and significance of an embryo are best determined by the individual or couple for whom it was produced, based on their individual or collective values, preferences and beliefs.

Despite this range of views, it is generally accepted that embryos are morally significant; that they are seen to be special and worth careful consideration. It is appropriate to think carefully about whether mitochondrial donation raises distinct social or ethical issues for the status of the embryo.

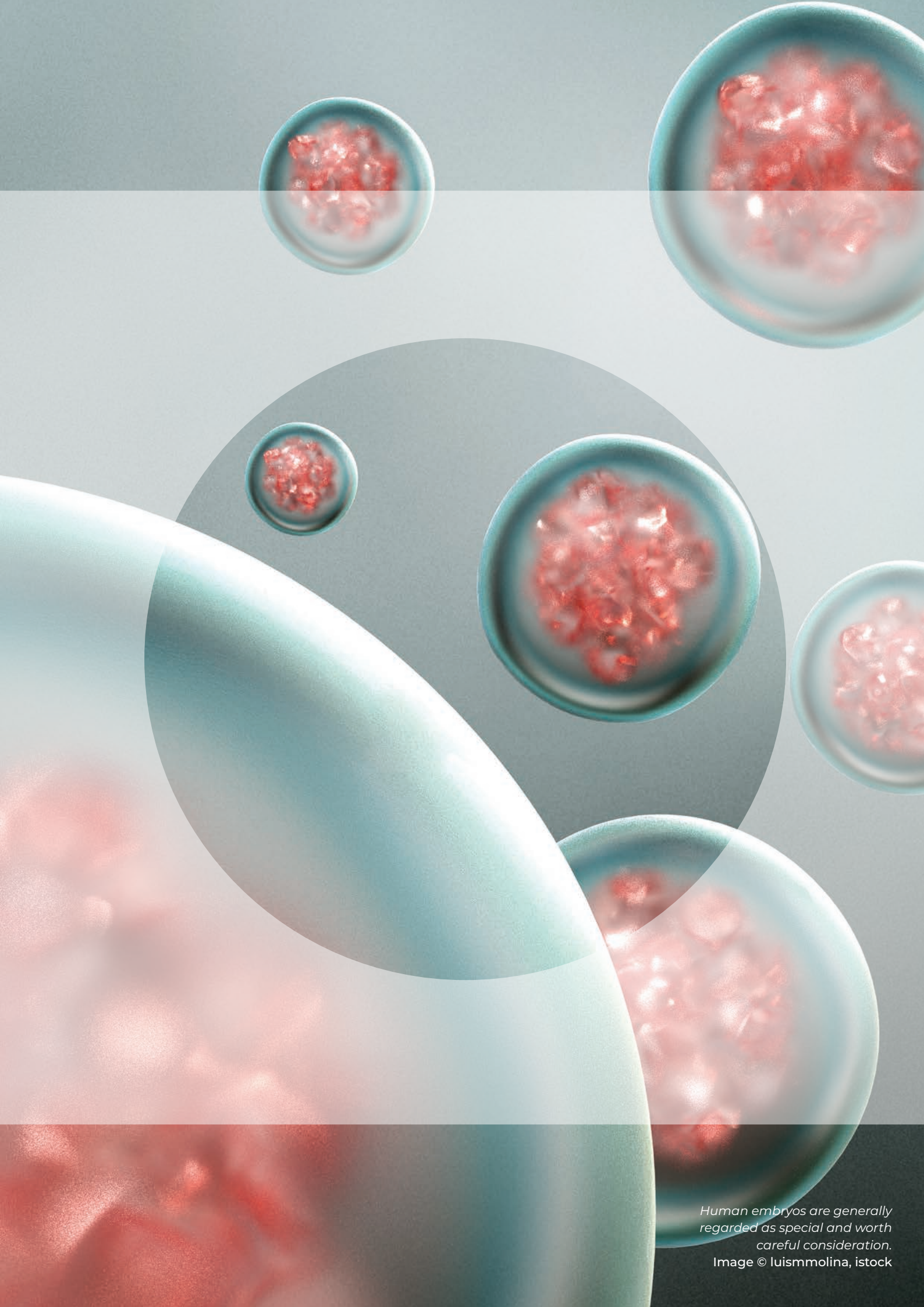
Existing assisted reproductive technology, such as IVF, involves the production of a human embryo outside the body, in a specialised laboratory. Many of the ethical issues associated with these existing technologies are also relevant to mitochondrial donation.

However, mitochondrial donation differs from traditional IVF as it involves producing an embryo that has mitochondrial DNA from an egg donor.

In the case of mitochondrial donation, the production of and research on embryos produced in this way is likely to be an essential step for translating research into a safe and effective clinical treatment. Opinions about the acceptability of producing embryos by fertilisation for use in research are likely to vary within the Australian community.

Some may argue that the production of such embryos is necessary to further our understanding of human development and the results of such research could contribute to innovations to treat and prevent disease. Others may argue that this production of embryos does not show respect for the embryo, nor reflect its special status.

An additional concern for women who are egg donors may be that their donated eggs will not necessarily result in live births. The need for further research and training on mitochondrial donation suggests that, at least initially, a significant proportion of donated eggs will not result in live births, but rather would be used and destroyed.



Human embryos are generally regarded as special and worth careful consideration.
Image © luismmolina, istock

Donor role and interests

Mitochondrial donation relies on the donation of eggs from women unaffected by mitochondrial DNA disease. This presents ethical and practical issues.

If it took place in Australia, mitochondrial donation would require women to donate eggs for research, training and treatment. These eggs would need to be suitable for reproductive purposes, and unaffected by mitochondrial DNA disease. Box 2 on page 10 describes the barriers to using a donor egg for people with mitochondrial DNA disease.

Respect, minimisation of harm and maximisation of benefit for all parties are relevant when considering the role and interests of women who are egg donors. As with egg donation for use in other forms of assisted reproductive technology, trade in eggs, informed consent, and coercion to donate may be issues of concern.

For egg donation to take place, consenting women are required to take medication to stimulate the ovaries to produce eggs, progress is monitored and egg collection is done in day surgery. The process takes just over a month and some women experience side effects. In Australia, it is an offence to buy or sell human eggs, sperm or embryos, although payment of reasonable expenses is allowed. However, there is a shortage of altruistic egg donors in Australia. Potential parents frequently travel to other countries to obtain donated eggs, where the woman donating an egg is usually paid. Accessing women overseas as egg donors has ethical and legal considerations specific to the country where the donor is recruited.

The pool of potential women as egg donors for mitochondrial donation could be further limited if it proves necessary to ensure that the mitochondrial DNA in a donor's eggs is compatible with the nuclear DNA of the woman requiring mitochondrial donation. This would mean that a compatible egg donor would need to be matched for each intended treatment.

The genetic relationship between an egg donor and a child born following mitochondrial donation is complex. The egg donor's nuclear DNA would not be present in a child born following mitochondrial donation, as only the donor's mitochondrial DNA would remain in the implanted embryo. Therefore, an egg donor may feel differently about the genetic connection to the child compared to the usual situation following an egg donation. However, the donor may feel connected to the child in other ways and may have an interest in knowing about any children born as a result of their donation.

Even if a woman who is an egg donor does not have interest in maintaining a relationship with any child born through mitochondrial donation, the experimental nature of mitochondrial donation means there may be a scientific need to retain and use information about that person.

Community considerations

The Australian community is likely to hold a range of opinions and perspectives about the use of mitochondrial donation. This includes concerns about the technology itself, who can access it and what the potential impacts on people now and in the future might be.

Mitchondrial donation is currently not in clinical use in Australia.

Australians may be concerned that if introduced, mitochondrial donation may result in heritable changes to the human genome. This includes the potential for long-term impact on future generations and the human gene pool.

The introduction of new technology such as mitochondrial donation can also raise community concerns about a 'slippery slope', where new technologies are gradually applied in a manner not originally intended or foreseen.

However, there are ways to restrict the introduction and use of new technologies through careful application of appropriate laws.

Further, it is standard practice for a new medical technology to be introduced cautiously. For example, if introduced to clinical practice, mitochondrial donation could be available only to parents determined by doctors to have a high chance of transmitting severe mitochondrial DNA disease to their children.

Social relationships and social context may affect a person's decision-making about mitochondrial donation. A public discussion about the technology and its clinical use must be sensitive to cultural and spiritual differences, and show respect for reproductive choices and individual autonomy. People seeking mitochondrial donation should be able to access accurate information.

If it were to be introduced in Australia, community attitudes towards the use of mitochondrial donation for research or in clinical practice may vary considerably. Such attitudes are likely to be shaped by a person's own particular set of values, preferences and beliefs, or those of their family and community.

If made available, some couples who might benefit from mitochondrial donation may choose to consider it, and others may not. Alternative options for prevention, diagnosis and treatment of mitochondrial DNA disease should continue to be investigated and, where appropriate, made available.

To support decision-making, people seeking mitochondrial donation are entitled to detailed, accurate, contemporary and relevant information about the proposed treatment and alternative options. Information giving and consent should be done in a timely manner, allowing adequate time for those involved to consider relevant issues. This should include information about the risks associated with the technique, the potential for unknown risks and any recommended or required follow-up.

Access to counselling by a professional with the appropriate training, skills, experience and competency to counsel in mitochondrial donation must be available. The interpretation of results related to mitochondrial donation and mitochondrial DNA disease can be complex and may change over time, and information giving should reflect this complexity.

Social relationships and social context may affect a person's decision-making about mitochondrial donation.
Image © Rawpixel, istock

The issue of who decides when a new technology should be made available for treatment is complicated. Families, clinicians, regulatory bodies and the community are all involved.

When considering the implementation of new technologies, it is important to develop a robust framework to support delivery of the technology.

If mitochondrial donation were to be implemented, the Australian Government would need to develop processes and policies to ensure that a person's eligibility to access mitochondrial donation is just, equitable, transparent, respectful and based on evidence.

Issues to consider include equity and fairness of access, how the treatment is funded, decision-making responsibilities, consent, privacy, data collection, and ongoing follow-up and reporting. A carefully developed framework requires further consultation with the public and/or key advisory groups before implementation.

Questions for public consultation

Specific questions

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?**

   There are various ways parents can avoid transmitting mitochondrial DNA disease to their children. However, in some cases, mitochondrial donation may be the only option for a woman to have a biologically related child without mitochondrial disease.

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

   The risks associated with mitochondrial donation are not fully understood. However, there are also potential benefits of this technology.

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?**

   Here, the risks and benefits of following an individual and tracking health over a lifetime may need to be considered.

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

   If introduced clinically, mitochondrial donation may affect future generations. Along with potentially preventing transmission of mitochondrial DNA disease, future generations may need ongoing follow-up and may carry heritable changes to their genomes.

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?**

   The technology applied in mitochondrial donation has different steps and biological materials compared to regular IVF.

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

   Mitochondrial donation, similar to some other assisted reproductive technologies, requires a woman as an egg donor. However it's only the mitochondria from that egg that are included in the embryo.

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?**

   Many people have an interest in the use and safety of reproductive technologies, including medical professionals, clinicians, scientists, prospective parents and the government.

Final questions

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?**

   Please explain your answer.

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?**

   Please explain your answer.

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?**

    Please explain your answer.

Glossary

assisted reproductive technology	The application of laboratory or clinical techniques such as IVF to gametes (eggs and sperm) and/or embryos for the purposes of reproduction.
blastocyst	A five to seven day old embryo, containing approximately 150 cells.
DNA	Deoxyribonucleic acid (DNA) is composed of four different types of smaller units (called nucleotides). The sequence of these nucleotides encodes the genetic instructions for the development, functioning, growth and reproduction of all known organisms. Changes (or 'mutations') to the sequence can introduce errors into the genetic instructions.
gamete	A sperm or egg.
genome	This paper refers to human, nuclear and mitochondrial DNA genomes. In these contexts, genomes refers to the complete set of genes/genetic material present in humans, or in each cell structure, respectively.
heritable changes	Changes that can be inherited by future generations.
heteroplasmy	Where a cell, tissue or person contains more than one mitochondrial DNA genotype, which may include a mix of healthy and mutated mitochondrial DNA. This may lead to mitochondrial DNA disease of varying severity.
homoplasmy	Where all copies of mitochondrial DNA in a cell, tissue or a person are identical. All the mitochondrial DNA may be affected by a mutation leading to mitochondrial DNA disease or all the mitochondrial DNA may be unaffected.
human embryo	The entity produced when fertilisation of a human egg by sperm is complete and a discrete organised biological entity exists but has not yet reached eight weeks of development.
IVF	In vitro fertilisation, a technology using eggs and sperm to create embryos in the laboratory.
mitochondria	Small structures inside cells important for energy generation and other cell functions. Mitochondria contain a small amount of DNA (see Box 1).
mitochondrial DNA	The DNA that resides in mitochondria rather than the nucleus of a cell. Unlike nuclear DNA, mitochondrial DNA is only inherited from the mother.
mitochondrial donation	A technique that involves the transfer of nuclear DNA into an egg or zygote that has a different population of mitochondria and has had its nuclear DNA removed. Also known as mitochondrial replacement therapy or mitochondrial transfer.
mutation	A change in the DNA sequence that can result in biological effects or disease.
nuclear DNA	The genetic material in the nucleus of a cell. DNA is assembled into chromosomes. A human cell usually has 46 chromosomes, 23 from each parent. Sperm cells and egg cells each have 23 chromosomes.
preimplantation genetic testing (PGT)	A procedure sometimes used in assisted reproductive technology to identify and screen for embryos affected by a genetic condition prior to transfer of the embryo to the woman's uterus.
transmission	The passing of genetic material from a parent to their offspring.
zygote	A fertilised egg before the first cell division. It contains genetic material from the mother and the father.

Australian Government
National Health and Medical Research Council

BUILDING
A HEALTHY
AUSTRALIA

Have your say by visiting
www.nhmrc.gov.au/mito

Online submissions are open from
23 September to 29 November 2019.

NHMRC

nhmrc.gov.au