Abstract
Should we proceed with mitochondrial replacement technique (MRT) research and clinical practice? There has been a lively debate on the topic in this journal, in which John Harris has argued in favour of this position and Inmaculada de Melo-Martin against it. This paper broadens the scope of this debate by presenting a richer account of the MRT phenomenon and by exploring some areas that naturally follow from Harris’s and de Melo-Martin’s discussion of the topic. First, I present what mitochondrial diseases and MRTs are. I expand on Harris’s portrayal of ‘mitochondrial disease’, which de Melo-Martin seems to follow. Secondly, I address how MRTs could prevent mitochondrial diseases, and if they would be effective in doing so. I do this by unpacking the differences between the types of MRTs. A detailed examination of the differences between MRTs shows that the ethical panorama is more complex than first thought. Thirdly, and finally, I present and defend the thesis that parents have strong reasons to disclose to their children that they were MRT-conceived. I show how both Harris’s and de Melo-Martin’s discussion of the ‘right to know our genetic origins’ can be complemented.

Keywords: mitochondrial replacement techniques, maternal spindle transfer, pronuclear transfer, mitochondrial replacement therapy, mitochondrial donation.

Introduction
There has been a lively exchange in this journal between Inmaculada de Melo-Martin and John Harris on the ethics of Mitochondrial Replacement Techniques (MRTs). Initially, Harris
advocated, here and elsewhere, for MRTs. He tried to show that the arguments against them are flawed and that MRT research and clinical practice should be supported because MRTs diminish suffering and increase wellbeing.

In response, de Melo-Martin argued that Harris’s arguments defending MRTs are found wanting and that we, in fact, should oppose them. She contended three things: that Harris only engaged with the weakest arguments that have been advanced against MRTs, that the resources that are used for MRT research and clinical practice should be repurposed for achieving worthier goals, and that MRTs are not necessary for women that have a mitochondrial DNA disease and want to have children genetically related to them, since they could have children through other means (e.g. adoption or egg donation).

Harris then replied to de Melo-Martin and defended his arguments. Firstly, he argued that in most instances both of them maintain the same position regarding de Melo-Martin’s objections against MRTs, and where they do diverge it is de Melo-Martin who is on the wrong side of the fence. Secondly, Harris contends that de Melo-Martin’s main criticism is off-target. He maintains that he was not making any claim about what priority we should give to MRT research and clinical practice, but that his sole aim was to assess if in principle MRTs, conceived solely as biotechnologies and abstracted from our social reality, are morally objectionable or not.

This paper constitutes a fourth act in this interplay of opinion. Here I will broaden the scope of the debate by presenting a richer account of the MRTs phenomenon: when we independently examine each of the techniques that have jointly have been labelled as MRTs (i.e. pronuclear transfer (PNT) and maternal spindle transfer (MST)) we realise that the ethical panorama is far more complex than it first appears. I will also develop areas that naturally follow from de Melo-Martin’s and Harris’s discussion of the topic.

This paper proceeds as follows. In the first section, I describe what mitochondrial diseases and MRTs are. This is important because in order to explain the differences between MRTs I need to expand on Harris’s portrayal of ‘mitochondrial disease’, which de Melo-Martin seems to follow. In the second section I address how MRTs could prevent mitochondrial diseases and if they would be effective in doing so. I do this by unpacking the differences between MRTs.
In the final section I present and defend that parents have strong reasons to disclose to their children that they were MRT-conceived, and show how this relates to Harris’s and de Melo-Martin’s discussion of whether there is such thing as a ‘right to know our genetic origins’.

1. Mitochondrial Diseases and Mitochondrial Replacement Techniques (MRTs)

Mitochondria are cellular organelles that generate the energy cells need to work properly. They are characterised by possessing their own DNA (mitochondrial DNA (mtDNA)), by only being inherited via the maternal line⁴, and their means of inheritance are non-Mendelian.⁵ Whereas nuclear DNA (nDNA) represents 99.9% of total human DNA, mtDNA only represents 0.1%.⁶

In both ‘Germline Modification and the Burden of Human Existence’ and ‘Germline Manipulation and Our Future Worlds’, Harris tells us that “[m]itochondrial disease can be very serious, causing conditions like Leigh’s disease, a fatal infant encephalopathy, and others that waste muscles or cause diabetes and deafness.”⁷ De Melo-Martin, in ‘When the Milk of Human Kindness becomes a Luxury (and Untested) Good. A Reply to Harris’ Unconditional Embrace of Mitochondrial Replacement Techniques’, does not provide a characterisation of mitochondrial diseases.

I will expand on Harris’s characterisation of ‘mitochondrial disease’, because for the sake of this discussion it is important to be specific about the details of what mitochondrial diseases are and how MRTs could prevent them. In a broad sense, there are two classes of mitochondrial diseases: mitochondrial diseases that are caused by problems in the mtDNA, and mitochondrial diseases that are caused by problems in the nDNA.⁸ This distinction is important because MRTs cannot be employed to deal with mitochondrial diseases caused by problems in the nDNA. MRTs can only be employed when the problems are caused by the genes in the mitochondria themselves. In other words, MRTs can only be employed when dealing with mtDNA diseases.

Mitochondrial DNA diseases are a group of neuromuscular diseases that cause suffering and premature death.⁹ Each mitochondrion contains various mtDNA copies. These various copies of DNA are not uniform: there exist various mutations among them, some of which are deleterious (i.e. mutations that prevent the mitochondrion from producing adequate levels
Mutations, both deleterious and non-deleterious, can be maternally inherited or created spontaneously. In some instances, deleterious mutant DNA can be the only type of mtDNA mitochondria possess. This is referred to as ‘homoplasmy’. Additionally, deleterious mutant DNA can be present in some mitochondria in addition to non-deleterious DNA, known as ‘heteroplasmy’.

Women with homoplasmic mtDNA containing deleterious mutations will always pass on the deleterious mutant mtDNA to their genetic offspring, irrespective of whether the kind of mutation will cause medical problems or not. Women with heteroplasmic mtDNA mutations (i.e. mtDNA that possesses deleterious and non-deleterious mutations), on the other hand, will pass on a mixture of mitochondria to their offspring; some of them without deleterious mutations and some of them with deleterious mutations. In this case the manifestation of the disease will depend on the deleterious mtDNA mutant load and the kind of mutation that is present. The amount of deleterious mutant mtDNA within each mitochondrion is caused by genetic bottlenecks during the division of mitochondria.\(^\text{10}\)

### 1.1 Mitochondrial Replacement Techniques\(^\text{11}\)

In his two papers on the subject of MRTs\(^\text{12}\) and his response to de Melo-Martin,\(^\text{13}\) Harris does not characterise the techniques that could be employed to avoid mtDNA diseases.\(^\text{14}\) This was not necessary as he was interested in discussing the ethics of germline modifications, and both types of MRT can cause such modifications when selecting for females. De Melo-Martin\(^\text{15}\) also does not present a characterisation of these techniques. In fact, she mentions only MST when discussing the safety issues related to MRTs, referencing Masahito Tachibana et al.’s research.\(^\text{16}\)

In de Melo-Martin’s case the absence of a proper characterisation of both MST and PNT is relevant because the differences between them yield different philosophical conclusions when considering issues about harm and identity, as Anthony Wrigley et al.\(^\text{17}\) and César Palacios-González\(^\text{18}\) have examined. I return to this point when I discuss how mtDNA diseases can be ‘prevented’ through MRTs.

The two most recently developed techniques that could help women afflicted with mtDNA diseases to have disease-free, genetically-related children are MST and PNT, as said
previously. Here I present a summarized version of how these techniques work.

In pronuclear transfer an oocyte from a woman with an mtDNA disease (Woman A) and an oocyte from a donor that possesses healthy mitochondria (Woman B) undergo IVF. The oocytes can be fertilized with sperm from Woman A’s partner or with sperm from a donor. After the sperm has fertilized the oocytes, and during the first hours, the nuclear material of both progenitors is enclosed in different membranes that are called the male and female pronuclei. On day one in the development phase, and prior to the fusion of the pronuclei, the pronuclei of both zygotes are removed. The pronuclei housed in the donor’s egg are discarded along with Woman A’s now enucleated cell (let’s remember that this cell possesses deleteriously mutated mtDNA). The pronuclei from Woman A, and her partner’s or donor’s pronuclei, are ferried into the now enucleated cell that was produced with Woman B’s oocyte (let’s remember that this cell possesses healthy mitochondria). The fused cell is transferred into the intended mother, or a surrogate, and if everything goes according to plan the embryo will develop normally.19

In maternal spindle transfer, assisted reproductive techniques are used to obtain eggs from the woman with an mtDNA disease (Woman A) and from a donor with healthy mitochondria (Woman B). The nDNA (which is found on one side of the oocyte in a spindle-shaped group) from both oocytes is removed. The chromosomes of Woman A are then ferried into Woman B’s enucleated egg. Woman B’s chromosomes and Woman A’s enucleated oocyte (let’s again remember that this cell possesses deleteriously mutated mtDNA) are discarded. The reconstructed egg, which has healthy mitochondria, goes through IVF and then is transferred into the intending mother, or a surrogate. The fused cell will go on to develop normally, if everything goes as planned.20

Two things bear mentioning. First, in both MST and PNT, it is possible that mitochondria with deleterious mutations could accidentally be transferred when the chromosomal carry-over is taking place. If this were the case, it is not impossible that the mtDNA disease could manifest in the child. Second, if MST and PNT are successful then the healthy mitochondria provided by the egg donor will be passed down via the maternal line to all subsequent generations. This means that if we select for females when using MST or PNT then the third-party mitochondria will be inherited when these women reproduce. If, on the other hand, we select
for males then the mitochondria will not be passed to the next generation.

2. How Do MRTs Prevent mtDNA Diseases?

Harris states that "MRT will prevent serious mitochondrial disease and the suffering it causes for women with mitochondrial disease, for their own children, and for countless future generations."21 I will now explore how MRTs could do this.

While Harris is in general optimistic about the development of MRTs, de Melo-Martin is sceptical. She argues against him that the resources invested in their development and translation into clinical practice only benefits a very small number of people:

[I]f reduction of the burdens of mitochondrial disorders were indeed the goal, research on basic and clinical studies on the causes, prevention, and treatment of these diseases will in all likelihood be more effective than research on MRTs. After all, even if all the women who could be eligible to use them did so –a big “if” indeed–, these technologies will have a relatively limited application. On the other hand, research on the diseases themselves and on more effective treatments for mitochondrial disorders would be of use to all of those suffering from these diseases.22

First, we need to be aware that MST and PNT prevent mtDNA diseases in two different ways. In most cases MST prevents mtDNA diseases by creating someone23 without the disease. MST, in most cases, does not cure someone of mtDNA disease. If who comes into existence is tied to our nuclear genetic makeup (i.e. if our numerical identity depends on our nuclear genetic makeup) then MST cannot be said to cure anyone, in most cases, because the fact that we decide to use MST alters the timing of conception and thus alters which gametes will fuse. For example, it is utterly improbable that the same sperm and egg would have fused in the following scenarios: (a) a couple decided to use MST, (b) the same couple decided to naturally reproduce, instead of employing MST. Furthermore, it is highly improbable that the same sperm and egg would have fused if the couple decided to use MST but chose to have the procedure one week after MST took place in scenario (a).

I have added the qualification ‘in most cases’ because there is the possibility that a single sperm and a single egg could have been chosen beforehand for the procedure.24 In this instance we could say that MST cured someone because the being that would result from the fertilization if MST did not take place and the being that would result from the fertilization if
MST did take place would possess the same nuclear DNA. This being the case, we have to conclude that in most instances MST prevents mtDNA diseases by creating someone without a mtDNA disease; and that only when we have, beforehand, selected a single sperm and egg can we say that MST prevents mtDNA disease by curing someone.

PNT, on the other hand, prevents mtDNA diseases by curing someone affected by them. If we accept, as before, that our numerical identity depends on our nuclear genetic makeup, then we have to accept that an embryo originated with X’s sperm’s nDNA, Y’s egg’s nDNA, and the faulty mtDNA W (found in Y’s egg) is one and the same embryo as that originated with X’s sperm’s nDNA, Y’s egg’s nDNA, and the healthy mtDNA Z (found in the donor’s egg). In this case we can affirm that PNT prevents mtDNA diseases by curing someone. Wrigley et al. reached this same conclusion:

In particular, PNT is a treatment which is attempting ‘pre-emptively’ to cure a person without affecting his or her identity. Thus, PNT is like, or is even a form of, gene therapy. MST, on the other hand, is a form of selective reproduction and has more in common with pre-implantation genetic diagnosis and pre-natal screening than it does with gene therapy.25

While this is the case,26 when we consider carrying out PNT in an embryo that we have already produced, if it were not for the fact that PNT was going to take place most probably that embryo would not have existed: the timing of conception would likely have changed and thus a different sperm and egg would have fused.

This clarification about how PNT and MST work is important because it tells us, specifically, how MRTs prevent mtDNA diseases, and because it shows that de Melo-Martin is mistaken when she assumes that MRTs would not effectively alleviate the burdens of mtDNA diseases. When de Melo-Martin speaks about the reduction of burdens of mitochondrial disorders she states that other means (such as basic and clinical studies on the causes, prevention, and treatment of these diseases) would be “more effective than research on MRTs”.27 However, if MRTs work as expected, then PNT and MST with preselected gametes would in fact be effective in treating mtDNA diseases if effective, here, means effective treatment of a condition. It is difficult to see how techniques that will successfully treat conditions resulting from mtDNA diseases can be labelled as non-effective.
At this point de Melo-Martin may argue that she is not talking about how effective MRTs are, or could be, as clinical procedures but how cost-effective they are, or could be, when compared with the cost-effectiveness of other treatments for mtDNA diseases, or mitochondrial diseases in general. If this is so then she is advancing an empirical claim that needs to be supported by empirical data, which she does not provide. Even if this data were available, then de Melo-Martin would still need to present a compelling argument to show that we have a moral duty to allocate the most resources to the most cost-effective research/treatment. And even if she presented such an argument, we would need to compare all medical research/treatments (assuming that this cost-effectiveness rationale is restricted to medical practice) to find out which would be the most cost-effective. This means that it is not completely certain at this point that research/treatment on MRTs would be halted under a cost-effectiveness paradigm.

The problem with the cost-effectiveness argument is that it artificially forces us to compare the cost-effectiveness of research into MRTs versus the cost-effectiveness of other possible treatments for mitochondrial diseases. To reach a conclusion, we need to compare all possible medical research/treatments and then see how research into MRTs fares. If this is what de Melo-Martin is arguing, then we have to accept that her case is at best inconclusive.

3. Reasons for Disclosure

A central topic of both Harris’s and de Melo-Martin’s work is whether MRT-conceived children have a right to know their genetic origins. It is important to note that whereas Harris states that “[a] problem is often raised about whether or not resulting children have a right or need to know the identity of the mitochondria donor”[emphasis added]28, de Melo-Martin focuses on “the alleged right to know one’s genetic origins? (...) Furthermore, I believe that talk of a right to know one’s genetic parentage imbues genetic information with very special significance and thereby contributes to promote problematic beliefs about genetic essentialism”.29 This distinction is important because there is a subtle difference between the right to know the identity of the mitochondrial donor and the right to know one’s genetic origins. The latter alleged right does not seem to necessarily imply a right to know the identity of those genetic origins.
Harris rejects the idea that there is such a right, which he labels as dangerous nonsense. He contends that if everybody had the right to know who their progenitors were we would need “universal paternity testing, with all the mischief that this would entail”. He anticipates “mischief” because of the phenomenon known as ‘non-paternity’. Non-paternity is a concept used to describe cases in which the biological father of a child is not who it is presumed to be. This belief can be held by the child, the presumed genetic father or the mother. According to Harris, non-paternity cases should not be a cause for concern and he even doubts the wisdom of correcting this state of affairs. He concludes that “[m]ore mischief and anxiety would certainly be caused by recognizing a right to know, or indeed a duty to disclose, all contributors to a given genome.”

De Melo-Martin is also unpersuaded by the supposed ‘right to know’ when considering the clinical application of MRTs, but, as she states, not for the reason that Harris presents: “my disinclination to make much of this alleged right to know one’s genetic origins has nothing to do with the phenomenon of non-paternity, but simply with the fact that no compelling grounds exist to support this presumed right.”

Even if we accept, for the sake of argument, that there is no such thing as a ‘right to know’ one’s genetic origins or the identity of the mitochondrial donor, as de Melo-Martin and Harris maintain, it must be noted that there are strong reasons to disclose to someone that she was MRT-conceived. It is important to emphasise that to disclose to someone that she was MRT-conceived is not the same as revealing who the ‘mitochondria donor’ is; it is similar to disclosing to someone that she was conceived with a donated gamete without revealing the donor’s identity. It is also important to point out that ‘to disclose to’ someone should not be understood negatively, as in ‘only if X asks about the way in which she was conceived will we tell her that she was MRT-conceived’. Here disclosure should be understood in a positive way: we have to ‘go and tell’ X that she was MRT-conceived.

An Ravelingien and Guido Pennings, when discussing the issues around the purported ‘right to know’ one’s genetic parents (and while referencing Vardit Ravitsky’s work on the topic), touch upon some of the reasons we have for disclosing to someone her genetic background:
Awareness of one’s genetic background is deemed necessary for a better understanding of and decision making about one’s health risks (...). Access to a full picture of one’s genetic background is also regarded as essential in terms of one’s psychological well-being and family relationships.\textsuperscript{36}

At this point, let’s set aside issues around how knowing that one was MRT-conceived affects one’s psychological well-being and family relationships.\textsuperscript{37} Instead, I will unpack the reasons parents have to disclose to their children that they were MRT-conceived. If parents disclose the conditions of their conception, these children, when they come to age, will have a better understanding of the health risks associated with their conception, or in this case the uncertainties about such health risks.

Knowing one’s \textit{genetic background} can be \textit{instrumentally good}: it provides information about oneself that might otherwise be nonobvious, and this information can be helpful for better assessing and managing health risks. Knowing that both my parents are recessive carriers of a Mendelian-inherited-type genetic condition provides me with information with which I can make better informed decisions regarding my lifestyle choices, decisions that could benefit my health in the long term, for example refraining from smoking. While whether I have a \textit{right} to such information is outside the scope of this paper, it is true that possessing such information is instrumentally good for me and that my parents have at least \textit{pro tanto}\textsuperscript{38} reasons to reveal it. This being the case, I can also affirm that \textit{possessing the information that I was MRT-conceived can be instrumentally good for me}, and thus that my parents also have \textit{pro tanto} reasons to reveal it. Furthermore, these reasons are \textit{stronger} because the way in which I was conceived is novel and thus could carry more health risks. It must be noted at this point that the advent and increasing popularity of personal genomic services (for example, 23andMe) could make it possible for someone to come to know that she was MRT-conceived without her parents having to disclose this to her.

An individual who knew about her MRT-conception could use this information to take better care of her health, and to enable her medical team to make better decisions when investigating the causes of an illness, for example. As John Appleby says:

\textit{Disclosure is important for at least two reasons: (1) the MRT-conceived person’s own medical welfare; and (2) knowledge of having been MRT-conceived enables persons}
to report any medical problems back to clinicians and researchers for the sake of the wellbeing of future generations who might be conceived via MRTs.\footnote{39}

He further provides an additional reason for disclosure: “it would save some children from the stress and anxiety of worrying about suffering from the same mtDNA disorders as their mothers.\footnote{40}

Harris and de Melo-Martin would agree, as would any other reasonable person, that regardless of the existence of a right to know one’s genetic origins or the identity of the mitochondrial donor there are strong pro tanto reasons for disclosing to someone that she was MRT-conceived. At this point we have to conclude that, while their discussion of the supposed ‘right to know’ is important and regardless of whether they are correct or not, we need to go beyond it and take into consideration other reasons for disclosure, as just presented.

\textbf{Conclusion}

De Melo-Martin and Harris have had a lively debate (which fits within the broader scope of recent work on the ethics of MRTs which deals with issues of identity,\footnote{41} transgenerational health risks,\footnote{42} the disclosure of MRT conception,\footnote{43} genealogical ancestry,\footnote{44} first in-human use,\footnote{45} the possible use of nonhuman oocytes for PNT,\footnote{46} and the anonymity status of the ‘mitochondrial donor’\footnote{47}) regarding the morality of MRT research and clinical practice. In this paper I have broadened the scope of the discussion regarding mitochondrial diseases and MRTs. I showed that de Melo-Martin’s cost-effectiveness argument is at best inconclusive.\footnote{48} I also showed that it is methodologically important to differentiate between mitochondrial diseases in order to understand which diseases MRTs could prevent, and how MRTs would do this.

Furthermore, I showed that using MST without preselected gametes prevents mtDNA disease by creating people without an mtDNA disease, rather than curing those who already have an mtDNA disease. PNT and MST with preselected gametes, on the other hand, can be said to cure mtDNA disease insofar as the numerical identity of the individual who will be ‘brought’ into existence is not altered. This is relevant in relation to de Melo-Martin’s claim that other research avenues might be more “effective” in treating mtDNA diseases, despite the fact that
if PNT and MST with preselected gametes were successful they would for certain be effective in treating mtDNA diseases.

Finally, I have shown that parents have strong pro tanto reasons for disclosing to their children that they were MRT-conceived. If they do so, their children will be able to make better decisions regarding their medical welfare (this issue is heightened by the fact that at least the first generation of MRT-conceived children would be born from an experimental technique), and medical teams will be better equipped to treat them. This shows that even if there is no such thing as a ‘right to know’, as Harris and de Melo-Martin maintain, there are important reasons to reveal to someone that she was MRT-conceived.

The richer account of MRTs that I have presented here show us that there is much more to be said about the morality of MRTs research and its clinical practice.

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4 The advent of in vitro gametogenesis could change this fact, given that one day it might be possible to generate eggs from male iPS cells and ES cells. See: Palacios-González C, Harris J, Testa G. Multiplex parenting: IVG and the generations to come. *Journal of Medical Ethics*. 2014;40(11):752–8.
It is worth mentioning that when referring to both Maternal Spindle Transfer and Pronuclear Transfer, Harris uses the term ‘Mitochondrial Replacement Therapy’ while de Melo-Martin and I use the term ‘Mitochondrial Replacement Techniques’.


There is another technique, which I will not discuss here, that has been suggested for preventing the clinical expression of mtDNA diseases: ooplasmic transfer. It involves injecting cytoplasm from a donor’s oocyte, with healthy mitochondria, into an oocyte with diseased mitochondria. See Brenner CA, Barritt JA, Willadsen S, Cohen J. Mitochondrial DNA heteroplasmy after human ooplasmic transplantation. *Fertility and Sterility*. 2000;74(3):573–8.

See note 2, de Melo-Martin 2016 (*Forthcoming*).

I am not unaware of the philosophical problems surrounding early embryo individuation (i.e. fission and fusion cases). Thus, when I talk about ‘curing someone’ I am not assuming that the embryo is a person, or that it cannot divide itself into two or more identical copies, or that these identical copies cannot fuse back together. Here ‘someone’ should be understood as a shorthand for ‘an embryo that can give rise to a body, or bodies, that can have, or not have, an mtDNA disease’.

I have explored this at length elsewhere, see note 18.

Even when Wrigley et al. recognised the differences between PNT and MST they failed to realise that MST with preselected gametes would also cure someone, as just explained.


34 How and when to disclose are questions beyond the scope of this paper.


44 See note 41, Baylis 2013;26(6):531–4; and note 37, Institute of Medicine of the National Academies 2016.


48 After this paper was accepted for publication, Tina Rulli’s paper “What Is the Value of Three-Parent IVF?” appeared on press. I contend that the argument that I have presented here against de Melo-Martin’s cost-effectiveness argument could equally be applied to Rulli’s cost-effectiveness argument, but I will have to leave a thorough examination of her argument for