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Mitochondrial Replacement Therapy and Identity

A Comment on an Exchange Between Inmaculada de Melo-Martin and John Harris

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In the January 2017 issue of *Cambridge Quarterly of Healthcare Ethics*, there is an exchange between Inmaculada de Melo-Martin and John Harris about the ethics of mitochondrial replacement therapy (MRT) occasioned by John Harris's January 2016 article in the journal.[1,2,3]

The debate between de Melo-Martin and Harris is wide ranging, but in this comment I want to focus on their disagreement about whether MRT is affecting the identity of the child who is born after MRT. Both de Melo-Martin and Harris seem to assume that this question has a straightforward answer: "Yes" for de Melo-Martin and "No" for Harris. More specifically de Melo-Martin argues that "susceptibility to disease and suffering"[4] is an identity-conferring trait, and that it is affected by MRT, and Harris counterargues that this entails that "all therapy and all disease is identity altering"[5] which he takes to be absurd. In his 2016 article, he argued that "no identity conferring features are transmitted by the mitochondria."[6] In this comment, I hope briefly to show (1) that the question is significantly more complicated than both seem to assume, and (2) that because they overlook important distinctions in relation to identity, they actually write at cross-purposes.

In this short comment I will not discuss when, if ever, questions about identity matter ethically.

The Creation of Identity

The first problem in the de Melo-Martin v. Harris exchange is that both participants elide an important distinction; that is, the distinction between changing an already existing identity, and creating or generating a specific identity. The question "is the identity of entity A that has been created by MRT determined by MRT?" is a different question than "is the identity of entity A, which already has an identity of the relevant kind, changed by entity A undergoing or having undergone MRT?" This is perhaps most clearly seen if the identity in question is personal, psychological identity; for example, Parfit's account of personal identity as overlapping, psychological continuity.[7] On this account, embryos do not have an identity, because they do not have a psychology; therefore,

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MRT cannot change their identity, but it can still determine it. Some mitochondrial diseases lead to intrauterine death, and so simply prevent the fetus from ever developing a Parfitian personal identity. And even in cases in which the child is born, MRT can determine its psychological identity. For example, if a child can either be born with or without maternally transmitted Leigh Syndrome, the psychological and therefore personal identity of that child will be determined by MRT, because Leigh Syndrome is characterized as being: "a progressive neurodegenerative condition, which particularly affects the brainstem, diencephalon, and basal ganglia. There are characteristic neuropathological features, but newer neuroimaging techniques can now easily detect these lesions in life. Clinically, these infants and children have signs of brainstem and basal ganglia dysfunction and often deteriorate in a stepwise manner."[8]

It is also plausible that some conditions that may determine which psychological identity an entity will develop do not change the identity of an entity that already has one. Let us imagine a condition that lowers cognitive ability by 50 percent, but does not change memories. It is plausible that a child born with that condition will develop a different psychological identity from the child that had been treated with something like MRT, but it is equally plausible that a 30-year-old adult who is struck by the condition will not change identity, because the adult preserves psychological continuity.

Identity of What?

The second problem in the de Melo-Martin v. Harris exchange is that neither of the participants defines which type of identity they are discussing. There are at least five different kinds of identity that could be in play (see Table 1), and whereas MRT does not affect some of these, it does affect others.

The first and most basic type of identity is numerical identity. Here we simply ask whether an entity is the same physical entity over time. What is important is the physical continuation of the entity, not its characteristics. Numerical identity plays a role in one important philosophical argument related to assisted reproduction. Am I numerically identical to the embryo that gave rise to me? Many would answer "Yes," but that is a potentially problematic answer because of the possibility of monozygotic twinning. If twinning occurs, the numerical identity relation is broken because numerical identity is transitive. Numerical identity between an embryo and a later child is only secure approximately 14 days after fertilization, when there is no longer a possibility of monozygotic twinning. It should be uncontroversial that MRT changes the numerical identity of the unfertilized or fertilized egg depending on which MRT technique is used. Parts of two prior "things" are brought together to create a new thing. The numerical identity of the child is therefore also changed. Against this, it could be argued that the mitochondria are only auxiliary to the entity, just as batteries are auxiliary to an electrical toy, and that no change in numerical identity takes place when the mitochondria are replaced.[9] The problem with this argument is that when we look at the actual techniques for MRT, they involve the replacement of all the cellular cytoplasm and machinery except for the nucleus or spindle, and the donor egg contributes by far the largest part of the resulting entity. We might then say that it is nevertheless the nucleus that is the important part, but that seems to involve an implicit reliance not on considerations of numerical identity, but on

Table 1. Types of Identity

Type of identity	Identity question	Conserved in mitochondrial replacement therapy?
Numerical identity	Is it the same entity that is born?	No, if we think that changes to the numerical identity of the egg change the numerical identity of the embryo
Genetic identity	Does the entity that is born have the same genetics?	Depends on the threshold for genetic identity
Phenotypical/ physiognomical identity	Does the entity that is born look the same (and will it continue to look the same)?	Yes, for some mitochondrial disorders No, for other mitochondrial disorders
Psychological identity	Does the entity that is born have the same psychology (and will it continue to have the same psychology)?	Yes, for some mitochondrial disorders No, for other mitochondrial disorders
Narrative/social identity	Is the entity that is born inscribed in the same social/familial narrative?	Yes, but…

considerations of genetic identity. Here is may be worth noting in passing that the very same technique that I here discuss as mitochondrial replacement is called "nuclear replacement" in discussions of cloning.

The second type of relevant identity is genetic identity. It is trivial that MRT works because it changes the genetic makeup of the egg, and thereby the zygote, embryo, fetus, child, and adult that emerge without mitochondrial disease as a result of the treatment. But does that constitute a change of genetic identity? This seems, as with many questions about genetic identity, to be a question of threshold that is susceptible to sorites considerations. It is difficult to say that changing one base pair in the genome changes genetic identity, and two still does not seem enough, neither do three and so on. One of the relatively common mitochondrial DNA (MtDNA) mutations is a 5k base deletion, but it is still a threshold question whether a change of 5,000 base pairs, in this case by addition, is enough to say that MRT affects genetic identity.[10,11] Compared with the whole human genome, 5k base is not much, but the mitochondrial genome is only approximately 14k base in total, so the change is approximately 35 percent of the mitochondrial genome. It might also be noted that MRT does change the detectable maternal mitochondrial lineage, and that might be sufficient to claim an effect on genetic identity.

The third type of relevant identity is phenotypical or physiognomical identity. Does the entity look the same or does MRT change the way the entity looks? When Harris writes in 2016 that "no identity-conferring features are transmitted by the mitochondria"[12] it is most likely this type of identity that is referred to, and similar statements have been made by the United Kingdom Medical Research Council and the Wellcome Trust in reply to a call for evidence from the Nuffield Council on Bioethics: "We do not believe the transfer of mtDNA raises issues around identity, since it does not carry any genetic

data associated with the normally accepted characteristics of identity. An analogy could be drawn with replacing the battery in a camera—the brand of the battery does not affect the functioning of the camera."[13]

It is true that mtDNA does not contain any genes that determine physiognomy in the normal child; that is, no genes for skin color, size of nose, curliness of hair, height, or any of the many other characteristics that together decide how someone looks. This does, however not mean that mitochondrial mutations cannot affect physiognomy. On the more trivial side, a number of the myopathy (muscle weakness) related mitochondrial mutations cause ptosis (droopy eyelids), but some cause more significant changes in looks. Kearns–Sayre syndrome is, for example, associated with short stature.[14,15]

The fourth type of identity is psychological identity, as discussed in the previous section. It is undoubtedly the case that MRT determines psychological identity in those cases in which the particular mitochondrial disease has a significant neurological component that impacts on cognitive and psychological development. But there are also types of mitochondrial disease that do not affect psychological identity.

The final type of identity to mention is social and narrative identity. What kinds of relationships does the entity have, and in which stories is it inscribed and does it become a participant? Some kinds of social relationships and thereby social identity are conserved in MRT (at least when a child is born, whether or not MRT had been used). The child will still, after MRT be "the first son of X and Y, a little brother to Z," and it will still be born into the same particular ethnic, social, and linguistic community. However, its social identity and narrative identity might diverge radically from the non-MRT identity over time. The child after MRT may become "the husband of A, and the father of B, C, and D" or "the graduate from Berkeley," whereas the child without MRT might have become "the child that X and Y tragically lost at age 4."

Why Does Precision About Identity Matter?

Considerations about identity are prominent in a range of bioethical debates. They are raised in relation to reproductive technologies including MRT and reproductive cloning, but also play a role in end-of-life debates concerning persons with dementia. However, given that there are many different types of identity that may be ethically relevant (the five outlined do not constitute an exhaustive list), and given that there are a number of different identity questions, there is great scope for elision among different types of identity and different identity questions. There is even greater scope for basing argument on one conception of identity in one context, and on another in a different context. Many authors who deny that MRT affects identity have previously argued that a child born after reproductive cloning is not identical to the person who is cloned. The argument that MRT does not affect identity can most plausibly be sustained on the basis of a genetic conception of identity, but accepting a genetic conception of identity would entail that the clone is identical to the cloned person. The argument that cloning is not identity preserving is most plausibly made on the basis of a psychological and/or social and narrative conception of identity. It is perhaps too much to expect perfect consistency in peoples' arguments over time, but using fundamentally different conceptions of identity in arguments within the same area of discourse (reproduction) to

sustain the desired conclusion should raise some concern.

Notes

1. de Melo-Martín I. When the milk of human kindness becomes a luxury (and untested) good. *Cambridge Quarterly of Healthcare Ethics*. 2017;26(1):159–65.
2. Harris J. How to welcome new technologies: some comments on the article by Inmaculada de Melo-Martin. *Cambridge Quarterly of Healthcare Ethics* 2017;26(1):166–72.
3. Harris J. Germline modification and the burden of human existence. *Cambridge Quarterly of Healthcare Ethics* 2016;25(1):6–18.
4. See note 1, de Melo-Martín 2017, at 160.
5. See note 2, Harris 2017, at 166–7.
6. See note 3, Harris 2016, at 11.
7. Parfit D. *Reasons and Persons*. Oxford: Oxford University Press; 1986.
8. Tuppen HA, Blakely EL, Turnbull DM, Taylor RW. Mitochondrial DNA mutations and human disease. *Biochimica et Biophysica Acta* 2010;1797(2):113–28, at 117.
9. I owe this argument to Iain Brassington.
10. See note 8, Tuppen et al. 2010, at 117.
11. Schapira AH. Mitochondrial disease. *The Lancet* 2006;368(9529):70–82.
12. See note 3, Harris 2016.
13. Nuffield Council on Bioethics. *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review*. London: Nuffield Council on Bioethics; 2012, at 53.
14. See note 2, Harris 2017.
15. See note 3, Harris 2016.