Is Mitochondrial Donation Germ-Line Gene Therapy? Classifications and Ethical Implications.

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ABSTRACT

The classification of techniques used in mitochondrial donation, namely their role as purported gene therapies, is far from clear. These techniques exhibit characteristics typical of a variety of classifications that have been used in both scientific and bioethics scholarship. We address two connected questions this gives rise to: (i) how should we classify mitochondrial donation techniques?; and (ii) what ethical implications surround such a classification? First, we outline how methods of genetic intervention, such as germ-line gene therapy, are typically defined or classified. We then consider whether techniques of mitochondrial donation fit into these, whether they might do so with some refinement of these categories, or whether they require some other approach to classification. To answer the second question, we discuss the relationship between classification and several key ethical issues arising from mitochondrial donation. We conclude that the properties characteristic of mitochondrial inheritance mean that most mitochondrial donation techniques belong to a new sub-class of genetic modification, which we call 'conditionally inheritable genomic modification' (CIGM).

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I. INTRODUCTION – DEFINITIONS, CLASSIFICATIONS AND SIGNIFICANCE

Discussions of the ethical and scientific aspects of interventions in the human genome are grounded in a range of conceptual bases. One of these is whether a change made to an individual's genome will target only them or their future children too. To date, human gene therapies tested in clinical trials have typically been only intended to induce genetic changes in the individual to whom they were given.[1] Safety and other concerns have meant that genetic interventions that could also affect the genetic makeup of a recipient's future children have not been condoned.[2]

[1] Recent research into embryo genome editing using CRISPR technology is one exception to this: P. Liang, et al. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein Cell* 2015; 6: 363-372; and X Kang, et al. Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *J Assist Reprod Genet*; doi: 10.1007/s10815-016-0710-8, advance online publication 6 April 2016. However these studies were not clinical trials, were not intended to lead to embryo transfer or subsequent implantation and took place in a jurisdiction that has permissive approaches to embryo experimentation. We do not consider these experiments further in this paper as they do not currently involve research into mitochondrial donation techniques.

[2] Gene therapy in man. Recommendations of European Medical Research Councils. *Lancet* 1988; 1: 1271-1272; UNESCO. 1997. Universal Declaration on the Human Genome and Human Rights. Available at: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html [Accessed 4 Jan 2016]: Art 24; Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of

Mitochondria are small organelles ('mini organs') in a cell's extra-nuclear cytoplasm.[3] They are essential to cell function and a range of serious conditions can result if a person has enough mitochondria with pathogenic gene changes (mutations).[4] While 'traditional' forms of gene therapy have tended to target genetic material in the nucleus of a cell, mitochondrial donation aims to substitute all of the mitochondria.[5] Substituted

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the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo, Spain: Council of Europe: Art. 13. For a summary of relevant national laws, see: T. Ishii. Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. *Reprod Biomed Online* 2014; 29: 150-155.

[3] For a summary of mitochondrial genetics, see: M.D. Bacchetta & G. Richter. Response to "Germ-line therapy to cure mitochondrial disease: protocol and ethics of in vitro ovum nuclear transplantation" by Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, and Michael J. Zinaman (CQ Vol 4, No 3). *Camb Q Healthc Ethics* 1996; 5: 450-457; J.J. Pasternack. 2005. *An Introduction to Human Molecular Genetics: Mechanisms of Inherited Diseases, 2nd ed*. Hoboken, NJ: John Wiley & Sons, Chapter 12; and P.D. Turnpenny. 2012. *Emery's Elements of Medical Genetics. 14th ed.* St Louis, US: Churchill Livingstone: 181-183, Chapters 2, 7 & 11.

[4] S. Adhya, et al. Mitochondrial gene therapy: The tortuous path from bench to bedside. *Mitochondrion* 2011; 11: 839-844. For a review of mitochondrial diseases, see: H. Cwerman-Thibault, et al. Mitochondrial medicine: to a new era of gene therapy for mitochondrial DNA mutations. *J Inherit Metab Dis* 2011; 34: 327-344; and Y.S. Ng & D.M. Turnbull. Mitochondrial disease: genetics and management. *J Neurol* 2016; 263L 179-91.

[5] We have used the term 'mitochondrial donation' in this paper as this matches the scope of the special issue, as well as being the predominant term used in the United Kingdom.

mitochondria may also be inherited by the individual's children, albeit in a non-standard way (which we discuss below). Mitochondrial donation therefore challenges existing presumptions around inheritable modifications to the genome and gives rise to a question over how these approaches should be classified.

There are three reasons why the significance of this classification is interesting from a bioethical perspective:

(i) The unique attributes of mitochondria offer an interesting opportunity for conceptual 'boundary work', particularly regarding how we understand related classifications such as germ-line gene therapies (GLT), or even what constitutes 'therapy';[6]

(ii) The way mitochondrial donation is classified may have implications for the acceptability of this technology if, for

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However, we note that other terms such as 'mitochondrial replacement', 'mitochondrial transfer', 'mitochondrial therapy' (or combinations thereof) are also used. Below, we coin our own term ('mitochondrial targeting techniques'; or MTTs), which we believe better suits the interventions and does not give rise to problems such as the fact that it is not merely mitochondria that are 'donated', but everything barring the pronuclei or spindle: T. Lewens. 2015. *The Biological Foundation of Bioethics*. Oxford: Oxford University Press: Chapter 1.

[6] Adams asserts the value to bioethics of having conceptual guidelines for genetic modification: H. Adams. A human germline modification scale. *J Law Med Ethics* 2004; 32: 164-173.

example, there are ethical concerns associated with a particular classificatory category; and

(iii) The classification may have implications for how policy should be made for mitochondrial donation, particularly with regard to the acceptability of allowing interventions that target mitochondria in germ cells and embryos.[7]

There are also a number of ways we might approach such a classification:[8]

(a) adopting narrow 'traditional' classifications and seeing how mitochondrial donation fits;

(b) assessing broad categories that take in a wider range of activities; or

(c) considering the 'core moral concern' arising in mitochondrial donation, by looking for similarities in the ethical issues that are associated with various categories of genome intervention and grouping them accordingly.

[7] While this is an interesting and important question, its full consideration is beyond the scope of this paper. For further discussion, see, e.g.: E. Juengst & E. Parens. 2003. Germ-line dancing: definitional considerations for policy makers. In *Designing our Descendants: The Promises and Perils of Genetic Modifications.* A.R. Chapman & M.S. Frankel, eds. Baltimore: The Johns Hopkins University Press: 20-36; and A.L. Bonnicksen. Transplanting nuclei between human eggs: Implications for germ-line genetics. *Polit Life Sci* 1998; 17: 3-10.

[8] Adapted from Juengst & Parens, Ibid, p. 23.

As we shall argue, none of these approaches provide us with a clear route to classification, as they each leave significant problems unaccounted for with respect to mitochondrial donation. Approach (a) will be too narrow, as characteristics of both mitochondria and mitochondrial donation mean that at least some forms of this intervention constitute neither somatic nor germ-line gene therapy as traditionally defined. Approach (b) proves too much, encompassing other non-genetic interventions; and Approach (c) highlights ways in which mitochondrial donation does not sit comfortably within existing classificatory categories due to concerns over its therapeutic status and risks. This leads us to claim the need for another approach, a new sub-class within genome modification that sits between (a) and (b), but which also accommodates concerns raised by (c). We term this sub-class 'conditionally inheritable genomic modification' (CIGM).

In developing our argument, we first describe the interventions under discussion. Second, we look at definitions of key classificatory concepts, such as the germline. We then consider how well mitochondrial donation actually fits these definitions (or modified versions thereof). Finally, we discuss the links between classification for mitochondrial donation and how we view the ethical status of mitochondrial donation, before explaining how CIGM will work as a category for classifying mitochondrial donation.

II. INTERVENTIONS TO PREVENT OR TREAT MITOCHONDRIAL DISEASE

Mitochondria are vital to cell function and have roles in energy generation as well as cell growth, differentiation and repair.[9] They have their own genome and are often present in thousands of copies in a cell.[10] Yet despite their essential role, mitochondrial DNA (mtDNA) is much more vulnerable to developing mutations than nuclear DNA.[11] Once a certain threshold in mutation load is reached, cellular function is affected, leading to disease.[12] Mitochondria are inherited in a matrilineal fashion: passed only from mothers to their children.[13]

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[9] Bachetta & Richter, op. cit. note 3; Pasternack, op. cit. note 3; Turnpenny, op. cit. note 3.

[10] A genome can be defined as the total genetic complement in a particular individual. It is also worth noting that mitochondria exist in a symbiotic relationship with nuclear DNA, in that several genes in a cell's nucleus are also involved in mitochondrial function: Turnpenny, op. cit. note 3, p. 126.

[11] This can lead to 'heteroplasmy', where cells contain a mix of mutated and non-mutated mitochondria. Cells that have mitochondria all of the one type are 'homoplasmic'. Women at risk of passing mitochondrial conditions to their children will have oocytes that are either homoplasmic or heteroplasmic. If the latter, then options such as prenatal diagnosis or pre-implantation genetic diagnosis may be available to them. A woman's mutation status could also have classificatory significance, which we discuss further below.

[12] Adhya, et al., op. cit. note 4, Cwerman-Thibault, op. cit. note 4; and Ng & Turnbull, op. cit. note 4.

[13] Spermatozoa contain only a few mitochondria and these are generally lost during fertilisation.

Given the impact of mitochondrial disease, a strong desire by couples to have genetically related children, and the difficulty in screening or selecting for mitochondrial disease prior to birth or embryo transfer, various methods of ameliorating mitochondrial disease in oocytes (eggs) and embryos are being investigated. The most prominent of these methods are Maternal Spindle Transfer (MST) and Pronuclear Transfer (PNT). [14]

Maternal Spindle Transfer (MST)

MST involves transferring the spindle (the nucleus in a particular stage of cell division) from an oocyte (egg cell) of a woman who will likely pass on a mitochondrial condition to her children into a donor oocyte provided by a healthy donor, which has had its nucleus removed (an enucleated oocyte). This oocyte is then fertilised using sperm from the woman's partner and, assuming other standard aspects of in-vitro fertilisation are satisfied (such as embryo quality on visual inspection), the egg will be implanted at an appropriate time in the hope that fertilisation will occur. In short, this technique leads to the creation of an oocyte with 'healthy' mitochondria

[14] Human Fertilisation and Embryology Authority. Undated. New techniques to prevent mitochondrial disease. London: HFEA. Available at: http://mitochondria.hfea.gov.uk/mitochondria/what-is-mitochondrial-disease/new-techniques-to-prevent-mitochondrial-disease/ [Accessed 4 Jan 2016]. An early protocol for MST was published with the alternate acronym of IVONT (in vitro ovum nuclear transplantation) in 1995: D.S. Rubenstein, et al. Germ-line therapy to cure mitochondrial disease: protocol and ethics of in vitro ovum nuclear transplantation. *Camb Q Healthc Ethics* 1995; 4: 316-339.

containing a nucleus obtained from an oocyte that has 'unhealthy' mitochondria. One of the most important features of MST from both classificatory and ethical perspectives is that the manipulation of mitochondria and gametes occurs *prior to fertilization*.

Pronuclear Transfer (PNT)

PNT adopts a similar 'replacement' approach to MST, but occurs at an early *embryonic* stage as opposed to in oocytes that are then fertilised. It involves fertilising an oocyte from an 'affected' woman with her partner's sperm to create a zygote (early embryo). The pronuclei (the nuclei of the sperm and egg during fertilisation, prior to them fusing) is then removed and placed into another zygote that has been created using a donor oocyte and the partner's sperm, but which has had the pronuclei removed. This embryo then begins to develop and is placed into the woman as for MST above. A crucial difference between PNT and MST is that in PNT the *manipulation occurs after fertilization*.

Other interventions to prevent mitochondrial disease

While MST and PNT are currently the primary modalities for mitochondrial therapy, they are not the only possibilities. Other approaches are more akin to 'traditional' gene therapy, targeting individual genes rather than organelles.[15] Advances in genome editing, for example, have raised the possibility that genes within the nucleus or mitochondria could be altered in either existing or future individuals.[16]

These other interventions could not be considered as mitochondrial donation, as no 'donation' takes place. However, given rapid advances in genome editing they may become more important over time. Accordingly, they will likely influence how we wish to classify interventions to prevent mitochondrial disease. For this reason, from hereon we refer to 'mitochondrial targeting techniques' (MTTs) rather than 'mitochondrial donation'. MTTs will group together any biomedical intervention that aims to alter the composition, structure or expression of mtDNA within a cell, whether via MST, PNT, genome editing or another method.

[15] Adhya, et al., op. cit. note 4.

[16] T. Morrow. 2015. Is gene editing mtDNA an alternative to mitochondrial replacement therapy? Sussex, UK: Ted's Blog. Available at: https://tedmorrow.wordpress.com/2015/04/24/is-gene-editing-mtdna-an-alternative-to-mitochondrial-replacement-therapy/ [Accessed 19 August 2015]; T. Ishii. Germline genome-editing research and its socioethical implications. *Trends Mol Med* 2015; 21: 473-481; and P. Reddy, et al. Selective elimination of mitochondrial mutations in the germline by genome editing. *Cell* 2015; 161: 459-469.

III. MTTs AS GENE THERAPIES?

The first stage in determining how we should classify MTTs requires an account of the distinguishing features of the relevant potential categories of classification. Once a consensus definition has been determined, these can be applied to MTTs to address the approaches posed in Part I.

One classificatory distinction of significant historical interest is between somatic and germ-line gene therapies.[17] Exploring this distinction not only raises the question as to whether MTTs might fall under the definition of somatic or germ-line therapy, but also whether they should be considered as gene therapies at all. This requires an initial definition of gene therapy.

Gene therapy can be defined as 'the correction of specific genetic defects in individual patients.'[18] It is often defined with reference to the use of

[17] R.F. Chadwick. 2009. Gene therapy. In *A Companion to Bioethics, 2nd ed.* H. Kuhse & P. Singer, eds. Oxford: Blackwell Publishing: 207-215.

[18] European Medical Research Councils, op. cit. note 2. The Human Genome Organisation (HUGO) offers a similar but more detailed definition of gene therapy as the 'correction or prevention of disease through the addition and expression of genetic material that reconstitutes or corrects missing or aberrant genetic functions or interferes with disease-causing processes': HUGO Ethics Committee. 2001. Statement on Gene Therapy Research. London: Human Genome Organization, cited by Chadwick, Ibid.

genes to 'treat or prevent disease',[19] to 'replace a faulty disease-causing gene',[20] or using a 'functioning gene to correct the effects of a disease-causing mutation.'[21] One challenge in classifying MTTs is that, if the term 'gene therapy' is actually intended to imply changes to *genes*,[22] some MTTs might be said to fall outside this definition, given that whole extra-nuclear organelles are substituted instead of targeting individual genes for alteration.[23]

[19] Genetics Home Reference. 2015. What is gene therapy? Washington, DC: US National Institutes of Health. Available at: http://ghr.nlm.nih.gov/handbook/therapy/genetherapy [Accessed 5 Jan 2016].

[20] Better Health Channel. 2011. Gene therapy. Melbourne: Victoria State Government. Available at: https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/gene-therapy [Accessed 5 Jan 2016].

[21] Your Genome. 2015. What is gene therapy? Cambridge: Wellcome Genome Campus. [Accessed 5 Jan 2016].

[22] D.R. Thorburn, et al. The pros and cons of mitochondrial manipulation in the human germ line. *Mitochondrion* 2001; 1: 123-127.

[23] The direction of 'therapy' to *an identifiable individual* may also be problematic; a point we consider further in Part IV below. It is also interesting to note that even some definitions of 'mitochondrial gene therapy' would appear to exclude MST and PNT; focusing instead on approaches that alter DNA or modify its expression within mitochondria: e.g. Adhya, et al., op. cit. note 4.

As to whether MTTs are gene therapies, there is some support for the view that mtDNA is not a significant component of the genome.[24] On this view, mtDNA is 'unlikely to change the physical and personality traits that define [a person],'[25] and will merely govern energy production.[26] However, as knowledge of the mitochondrial genome increases, the recognised contribution of mtDNA to human traits is also growing. Mutations in mitochondrial DNA have been linked to problems with bodily systems such as the brain, kidneys, the heart, endocrine system and skeletal muscles. They have also been linked to specific diseases such as Parkinson's Disease, macular degeneration and response to traumatic brain injury.[27]

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[24] e.g. Public Health Directorate / Health Science and Bioethics Division. 2014. Mitochondrial Donation: A consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child. London: Department of Health. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf [Accessed 26 Aug 2015]: 13. The implication here being that if a change is not significant, it does not constitute gene therapy (of any kind).

[25] C.T. Moraes, et al. Manipulating mitochondrial genomes in the clinic: playing by different rules. *Trends Cell Biol* 2014; 24: 209-211: 211.

[26] Nuffield Council on Bioethics. 2012. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. London: Nuffield Council on Bioethics. Available at: http://nuffieldbioethics.org/project/mitochondrial-dna-disorders/ [Accessed 4 Jan 2016].

[27] Thorburn et al., op. cit. note 22; H. Li, et al. Physiology and pathophysiology of mitochondrial DNA. *Adv Exp Med Biol* 2012; 942: 39-51; G. Hudson, et al. Two-stage

Additionally, the nature and effects of mitochondrial disease are significant and indeed are the whole reason MTTs are under development. To this end, given the significance of mtDNA, MTTs would seem to fall within the scope of the definitions of gene therapy provided above.

Moreover, given this significance of mtDNA in determining our physical constitution, it is reasonable to *intend* MTTs to be *a form* of gene therapy and so what may be needed is for definitions of gene therapy, or their variations, to reflect the fact that the target for change is not only a gene. Like 'traditional' gene therapy, MTTs are being developed to correct a genetic condition and researchers in this area are describing them as 'gene therapy'.[28] That said, some scholars have also pointed out the limits of the

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association study and meta-analysis of mitochondrial DNA variants in Parkinson's disease. *Neurology* 2013; 80: 2042-8; H. Bulstrode, et al. Mitochondrial DNA and traumatic brain injury. *Ann Neurol* 2014; 75: 186-95; M.C. Kennedy, et al. Mitochondrial DNA variants mediate energy production and expression levels for CFH, C3 and EFEMP1 genes: implications for age-related macular degeneration. *PLoS One*, 2013; 8: e54339; A.L. Bredenoord, et al. Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues. *Hum Reprod Update* 2008; 14: 669-678.

[28] e.g. M. Tachibana, et al. Towards germline gene therapy of inherited mitochondrial diseases. *Nature* 2013; 493: 627-631; and S. Di Mauro, et al. Approaches to the treatment of mitochondrial diseases. *Muscle Nerve* 2006; 34: 265-283.

term ‘gene therapy’.[29] With this in mind, the next step is to consider what kind of modification MTTs might be.

Somatic gene therapy

The term ‘somatic’ as we now use it comes from the German word ‘*somatische’*, as coined by embryologist August Weismann in 1885.[30] He distinguished *somatische* cells from those that contained *keimplasma* (germ plasm) which, at the time, was considered responsible for passing on traits. While we now know that genes (and the moderation of their expression) explain how many traits are transmitted between generations, Weismann’s distinction between cell types has persisted.

Somatic gene therapy occurs where ‘foreign genes are inserted into a target cell line (for cells other than germ cells) to correct a genetic defect.’[31] There is thus no intention that the introduced material will be passed on to the recipient’s descendants, although an off-target

[29] D.B. Resnik & P.J. Langer. Human germline gene therapy reconsidered. *Hum Gene Ther* 2001; 12: 1449-1458. We discuss this further below.

[30] A. Weismann. 1891. *Essays upon Heredity and Kindred Biological Problems*. Oxford: Oxford University Press., cited by Juengst & Parens, op. cit. note 7, p. 21. It should be noted that the root of this term is the Greek 'soma' meaning 'the body', as distinct from ‘the soul/the mind,’ although in this application it was taken to mean ‘the body of an organism’ as distinct from its ‘reproductive cells.’

[31] I. Kerridge, et al. 2013. *Ethics and Law for the Health Professions, 4th ed*. Sydney: The Federation Press: 1089.

therapeutic insertion may inadvertently augment an individual's germ-line too.

Germ-line gene therapy (GLT)

The germ-line is genetic material that is inheritable by children from their parents.[32] GLT has therefore been described as 'the insertion of a normal gene into the germ-line ... to replace a defective or lethal gene...'[33]

There are a number of targets for these inheritable changes. Early definitions of GLT pertained directly to genetic alterations of gametes or germ cells.[34] Later descriptions expanded the array of target cells from just

[32] M.S. Frankel & B.T. Hagen. 2011. Germline therapies. London: Nuffield Council on Bioethics. Available at: http://nuffieldbioethics.org/wp-content/uploads/Germline_therapies_background_paper.pdf [Accessed 15 June 2015]: 1.

[33] Kerridge et al., op. cit. note 31: 1090. Frankel & Chapman offer a similar definition, that mentions 'transfer of genetic material' rather than inserting genes: M.S. Frankel & A.R. Chapman. 2000. Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious and Policy Issues. United States: American Association for the Advancement of Science. Available at: http://www.aaas.org/sites/default/files/migrate/uploads/germline.pdf [Accessed 18 Aug 2015]: 61.

[34] e.g. Anderson described it as 'the correction of the disorder in the gametic cells of the patient so that children of the patient would receive the normal gene': W.F. Anderson. Human gene therapy: why draw a line? *J Med Philos* 1989; 14: 681-693: 682; while Walters and Palmer used the slightly simpler description of 'a therapeutic genetic

gametes to also encompass pre-embryos, early embryos, or changes made within an adult that also affected gametes.[35]

The key distinction between somatic and germ-line gene therapy is that germ-line interventions will *effect changes in the descendants* of those who have received the change. The therapeutic target is a child of the 'affected' individual, not necessarily the individual whose gametes are being used. Some commentators emphasise the permanence of the genetic change through generations[36]; an attribute of GLT that is of particular relevance to MTTs.

Alternative classifications: IGM and HGLGM

Limits of the above classifications, such as their focus on altering discrete *genes*, have already been described. To this end, alternative classifications have emerged.

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alteration in germ-line cells.': L. Walters & J.G. Palmer. 1997. *The Ethics of Human Gene Therapy*. New York: Oxford University Press: 62.

[35] e.g. Council of Europe, op. cit. note 2; Juengst & Parens, op. cit. note 7; Bredenoord, et al., op. cit. note 27; and J.C. Fletcher & W.F. Anderson. Germ-line gene therapy: a new stage of debate. *Law Med Health Care* 1992; 20: 26-39.

[36] e.g. E.M. Berger & B.M. Gert. Genetic disorders and the ethical status of germ-line gene therapy. *J Med Philos* 1991; 16: 667-683.

Some alternative classifications define an intervention by its cellular target (somatic or germ cell[37]; or the particular part of the cell[38] - as opposed to targeting a gene) and its actual effect.[39] However, cellular targets can be hard to control. And waiting to observe an effect prior to categorising an intervention such as MTTs will be problematic for both ethical and policy analysis, as if categorisation is relevant to these activities then post-hoc classification will not be helpful. Hence, in what follows we take a prospective approach to classification of MTTs.

A more promising conceptualisation is Inheritable Genetic Modification (IGM). One definition of IGM is:

> …any *biomedical intervention* that can be expected to enable us to modify the genome [such] that the subject of the intervention *can* transmit [it] to her or his offspring selectively.[40]

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[37] M. Lappé. Ethical issues in manipulating the human germ line. *J Med Philos* 1991; 16: 621-639.

[38] Bacchetta & Richter, op. cit. note 3.

[39] e.g. Lappé, op. cit. note 37.

[40] Juengst & Parens, op. cit. note 7, p. 33; emphasis added. This definition is similar to those offered by Rasko et al: J.E.J. Rasko, et al. 2006. Is inheritable genetic modification the new dividing line? In *The Ethics of Inheritable Genetic Modification: A Dividing Line?* J.E.J. Rasko, et al., eds. Cambridge: Cambridge University Press: 1-15; and Frankel & Chapman, op. cit. note 33: 2. The use of 'biomedical intervention' is an important limitation in that it rules out other kinds of intervention, such as partner choice, that could otherwise be considered IGM.

IGM, it is claimed, 'more clearly captures the variety of ways in which genetic information can be passed to the next generation.'[41] That is, IGM allows recognition that emergent interventions such as MTTs can fall outside traditional definitions of and distinctions between somatic and germ-line gene therapy.

The other advantage is IGM's focus on *inheritable modifications,* rather than *germ-line therapies.* This focuses on the effects of the intervention rather than its biological properties.[42] As we discuss in section IV, there may also be forms of MTT which, due to the Non-Identity Problem, are not therapeutic in that they will not benefit a particular individual. Further, like other genetic interventions, MTTs could one day be used to *enhance* rather than to treat.[43]

The above definition of IGM is, however, a broad classificatory category and as such may be overly inclusive. It may, for example, encompass incidental changes to the epigenome[44] caused by, for example, some biomedical interventions such as prescription drugs. This will conflate

[41] Frankel & Hagen, op. cit. note 32, p. 5.

[42] Rasko, et al., op. cit. note 40.

[43] Ibid. We discuss these latter two considerations in more detail in Part IV below.

[44] The epigenome comprises non-genetic but nevertheless inheritable chemical modifiers of gene function.

interventions using techniques of molecular biology with other biomedically-mediated changes. This is undesirable for both conceptual and pragmatic reasons; such as maintaining separate regulatory processes, but will be mitigated by narrower definitions of IGM.[45]

Resnik and Langer offer a conceptual refinement that is also useful.[46] In describing what they term 'human germline *genome* modification' (HGLGM; emphasis added), they recognise that altering a genome can be done at more than the level of the gene. This is implied in the above definition of IGM but is not reflected in the name ('inheritable *genetic* modification'). Resnik and Langer also recognise that the distinctions between therapy, prevention and enhancement are not absolute. HGLGM can be said to have occurred when 'a genome [is created] that would not have occurred otherwise' and that such creation is intentional.[47] However HGLGM is also narrower than IGM in that it focuses on the *target* of intervention (the germ-line), whereas IGM is framed according to the intended effect: whether the change is *inheritable*.

[45] e.g. Bredenoord, et al., op. cit. note 27. At p. 670 they describe IGM as: 'new genetic material... [being] introduced into the gametes (or early embryo).' They add that 'This genetic modification is not only passed on to the child, but *also to subsequent generations*.' We claim that a definition of IGM is undesirable if any human or environmental intervention could end up being classified as IGM.

[46] Resnik & Langer, op. cit. note 29.

[47] Ibid, p. 1453. They expressly include techniques such as (what are now known as) PNT and MST as HGLGMs and exclude somatic methods.

As we discuss further below, a modified concept incorporating elements of both IGM and HGLGM, which also accounts for the distinguishing features of mtDNA inheritance, may be the best classificatory tool for MTTs.

The variables of classification

We have considered a range of definitions and classifications of interventions into the human genome. Yet these classifications have not yet allowed us to consider the properties of MTTs in depth. Here, we present six variables in approaches to genetic intervention which will help inform how MTTs may be classified.

First is the *target* of the intervention.[48] In more traditional approaches, the target for genetic modification has been genetic material, usually a single gene, in the nucleus. In MST and PNT, the target for augmentation is a whole organelle outside of the nucleus. The implications of this could, for example, lead to these particular MTTs being viewed instead as 'organelle transplants' and thus falling outside the scope of gene therapy altogether.[49]

[48] Rubenstein, et al., op. cit. note 14; Bonnicksen, op. cit. note 7; Juengst & Parens, op. cit. note 7.

[49] e.g. NESCI. 2008. Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation. Newcastle: North East England Stem Cell Institute. Available at:

Some have used the interventional target to distinguish MTTs. For example, the United Kingdom (UK) Department of Health has defined genetic modification as something that 'involves the germ-line modification of *nuclear* DNA (in the chromosomes).'[50] Yet while this makes for a clear distinction and may serve useful policy purposes, some may also claim that this overlooks the relationship between nuclear DNA and mtDNA, including how mitochondrial haplotypes may influence nuclear

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http://www.ncl.ac.uk/nesci/assets/docs/NESCIbriefon2008HFEbill-MitochondrialTransplants-Vers01-6.pdf [Accessed 3 Jul 2015]; Bredenoord, et al., op. cit. note 27; Moraes, et al., op. cit. note 25; Frankel & Hagen, op. cit. note 32. The United Kingdom Department of Health have also endorsed an analogy between mitochondria and a 'battery pack': Public Health Directorate / Health Science and Bioethics Division, op. cit. note 24, p. 13; c.f. Juengst & Parens, op. cit. note 7. Opposing this idea, Juengst and Parens claim (and we agree) that 'a human germ-line cell [that has undergone therapy] has had part of its genome … replaced in a way that will be inherited by its descendants': at p. 30 – thus aligning more with the concept of gene therapy/genetic modification than transplantation. Additionally, in most cases of organ donation it is only a very rare occurrence to pass genetic changes to future generations.

[50] Public Health Directorate / Health Science and Bioethics Division. 2014. Mitochondrial Donation: Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child. London: Department of Health. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf [Accessed 25 Aug 2015]: 15. Emphasis added. The UK Government accepts that PNT is germ-line modification, but rejects that it is *genetic* modification.

DNA expression.[51] It is also inconsistent with views on what constitutes genetic modification (synthesised above) and other policy statements that categorise MTTs as genetic modifications while simultaneously classifying some MTTs as IGMs.[52]

Second, the *method* of gene modification can also differ. In 'standard' approaches to gene therapy, recombinant DNA technology tends to be used. This uses restriction enzymes - chemicals that cleave DNA by

[51] E.H. Morrow, et al. Risks inherent to mitochondrial replacement. *EMBO Rep* 2015; 16: 541-544; K Reinhardt, et al. Mitochondrial replacement, evolution, and the clinic. *Science* 2013; 341: 1345-1346; D.B. Sloan, et al. Mitonuclear linkage disequilibrium in human populations. *Proc. R. Soc. B*, 282: 20151704; Bredenoord, et al., op. cit. note 27. Note, however, that this debate is not settled. While evolutionary biologists continue to raise concerns about how MTTs may disrupt the regulation of nuclear gene expression by mtDNA, MTT researchers involved point to the main experiments leading to this concern having been undertaken in fruit flies (which have poor evolutionary conservation with humans) and inbred mice (which again may be a poor model): personal communication - Prof David Thorburn, 18 & 22 September 2016. Some propose using haplotype-matched mitochondrial DNA in MTTs: N. Gemmell and J.N. Wolff. Mitochondrial replacement therapy: Cautiously replace the master manipulator. *BioEssays* 2015 37: 584–585; and K.J Dunham-Snary and S.W Ballinger. Mitochondrial-nuclear DNA mismatch matters. *Science* 2015; 349: 1449-1450.

[52] See, for example: National Academies of Sciences, Engineering, and Medicine. 2016. Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations. Washington, DC: The National Academies Press. Available at http://www.nap.edu/21871 [Accessed 4 Feb 2016], Chapter 3, p.7ff. We discuss this approach further below.

recognising certain DNA sequences. However, MST and PNT do not involve any alteration at the level of DNA (although other forms of MTTs may). The UK Department of Health highlighted this distinction, pointing out that:

> The key consideration is that these techniques only substitute, rather than alter, a very limited number of unhealthy genes … of cells with healthy ones.[53]

Another method-oriented distinction relevant to methods of MTT that involve genome editing is that the therapeutic vector (the system that delivers the intervention) would only need to be expressed for a short time.[54] This would destroy the mutated mitochondria in a target cell (whether somatic or germ-line), and the 'healthy' mitochondria would proliferate.[55] Changes to nuclear DNA, in contrast, would need to be continuously active for the altered gene expression to persist.

A third demarcation in gene therapy definitions is the *mechanism of inheritance* of the introduced change. In classic approaches to gene therapy, the changes to the genome would follow Mendelian inheritance.[56]

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[53] Public Health Directorate / Health Science and Bioethics Division, op. cit. note 24: 13.

[54] Moraes et al., op. cit. note 25.

[55] Note that this would only work if the target cell contained a mix of healthy and mutated mitochondria (heteroplasmy).

[56] That is, the changes would follow rules of genetic segregation first described by Gregor Mendel. See: Pasternack, op. cit. note 3, Chapter 3.

However, changes in mitochondria following MTTs would only persist through subsequent generations if a female child went on to have female children.[57] Further, the cell division process during oocyte creation and embryogenesis is considered to lead to a 'bottleneck' effect that influences which mitochondria are passed from a mother to her children.[58] This, combined with their comparably high rate of mutation and the uncertain way in which mitochondria are distributed during cell division,[59] means that interventions in a cell's mitochondria will impact future generations differently (and often with less certainty) than changes to nuclear DNA. We call these properties their 'conditional inheritance'. There is no other mode of genetic inheritance that has the same conditional effects as that seen in mitochondria.[60]

[57] This also raises an interesting point about inheritability and subsequent likely impact on future generations that we return to when considering the ethical implications of MTT.

[58] J. Poulton, et al. Transmission of mitochondrial DNA diseases and ways to prevent them. *PLoS Genet* 2010; 6; H.S. Lee, et al. Rapid mitochondrial DNA segregation in primate preimplantation embryos precedes somatic and germline bottleneck. Cell Rep 2012; 1: 506-515; and I.J. Wilson, et al. Mitochondrial DNA sequence characteristics modulate the size of the genetic bottleneck. *Hum Mol Gen* 2016; 25: 1031-41.

[59] H.J.M. Smeets. Preventing the transmission of mitochondrial DNA disorders: selecting the good guys or kicking out the bad guys. *Reprod Biomed Online* 2013; 27: 599-610.

[60] Inheritability of mitochondrial mutations depends on the biological sex of the parent, bottleneck effects, rates of mutagenesis and chance (and taking it as given that reproduction is definitely going to take place). Regarding matrilineal inheritance, one of the interesting aspects of how we might wish to regulate or generate policy for MTTs is that, in order to allay fears of unforeseeable consequences of altering the germ-line for

Fourth, the *kind and degree of change* could be relevant. The substitution/alteration distinction already mentioned could be said to be a difference in kind. Additionally, we might point to the size of the mitochondrial genome, which comprises only 37 genes with a total length of 16.5kb. MTTs may therefore consist of a smaller overall change when compared to interventions targeted to the nucleus, particularly if a large gene were altered. However, we also recognise that relying on degree of change alone may be problematic. Even though the size of the genome is small, oocytes can contain around 200,000 copies of the mitochondrial genome – only 0.2% of the number of genes, but 50% of the amount of DNA.[61] Further, as Smeets points out, there are scientific scenarios for MTT in which a recipient oocyte or embryo ends up having no new mtDNA sequences at all.[62]

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future generations, a policy of only allowing male children to be born through this method might be implemented: National Academies of Sciences, Engineering, and Medicine, op. cit. note 52, Ch 4, p6-7; A.L Bredenoord, et al. Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection? *Hum Reprod* 2010; 25: 1354-1360; J.B. Appleby. The ethical challenges of the clinical introduction of mitochondrial replacement techniques. *Med Health Care Philos* 2015; 18: 501-514. This would have the effect of a policy initiative changing the way in which we might classify MTTs by simply blocking the possibility of inheritable changes for future generations.

[61] Personal communication, Professor David Thorburn.

[62] This could occur, for example, if a female relative (or any other oocyte donor who had the same haplotype) provided oocytes to an intending mother who had heteroplasmic

Fifth, the *risk of the change* may also be relevant. In approaches that use recombinant DNA methodology to target the nucleus, it could be argued that the risk is higher due to possibilities such as a change occurring in the wrong gene.[63] Debates continue about the safety of techniques such as MST and PNT.[64] Nevertheless, regulations permitting their use in highly regulated environments have been introduced in the United Kingdom; and other jurisdictions may soon follow.

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mitochondria: Smeets, op. cit. note 59. The result would be to enrich a mitochondrial genotype that is already present in the intending mother's germ-line, rather than the resulting individual receiving any 'new' sequence. However, heteroplasmy is necessary for this because if the intending mother was homoplasmic for the relevant mutation, then she would only have mutated mitochondria to enrich. Smeets uses this scenario to claim that not all MTTs will change the germ-line; a point we return to in Part V below.

[63] e.g. An 'off-target' effect is one such concern: H. O'Geen, et al. How specific is CRISPR/Cas9 really? *Curr Opin Chem Biol* 2015; 29: 72-78.

[64] Morrow, et al., op. cit. note 51; Reinhardt, et al, op. cit. note 51; G. Hamilton. The mitochondria mystery. *Nature* 2015; 525: 444-446; A.L. Bredenoord & P. Braude. Ethics of mitochondrial gene replacement: from bench to bedside. *BMJ* 2010; 341: c6021; c.f. NESCI, op. cit. note 49; P.F. Chinnery, et al. The challenges of mitochondrial replacement. *PLoS Genet* 2014; 10: e1004315; H. Ma, et al. Metabolic rescue in pluripotent cells from patients with mtDNA disease. *Nature* 2015; 524: 234-238; L.A. Hyslop, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. *Nature* 2016; 534: 383-6; and M. Yamada, et al. Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes *Cell Stem Cell* 2016; 18: 1-6.

Finally, the *intentionality* of the change may be different; although this is a contentious variable. It might be claimed that with more 'traditional' forms of germ-line gene therapy there is an intention to effect change for future generations.[65] In contrast, MTTs might instead aim at preventing the somatic cell deficiency in the oocyte or embryo, with any change to future generations being an unintentional 'by-product'. However, this distinction is disingenuous in that the inheritability of MTTs is widely understood.

These variables of classification of MTTs can be summarised as follows:

	'Traditional' approach…	**Comparator**
Target	Nuclear DNA	Mitochondria (MT)
Method	Recombinant DNA	MT substitution or replacement
Mechanism of inheritance	Mendelian	Non-Mendelian
Kind and degree of change	Alteration; Variable	Replacement; Small or Nil
Asserted Risk	Higher	Lower
Intentionality	Intentional effect for future generations	'Unintended by-product' of attempt to prevent embryo's somatic cell deficiency?

[65] Juengst & Parens, op. cit. note 7, raise (but do not endorse) this point when considering the differences between somatic and germ-line gene therapy: see pages 22-3. We have applied their point about intentionality to MTTs.

Applying the variables of classification to MTTs

Our discussion illustrates that there are ongoing tensions in classifying interventions in the human genome. We will now consider how MTTs might be classified in light of this.

At first glance, only MTTs that aim to treat the non-germ cells of existing individuals with mitochondrial disease would satisfy the definition of *somatic gene therapy*. As there is no such therapy at present, it appears that MTTs are unlikely to be classified as somatic therapies. Yet two counter-points can be considered before somatic MTTs are dismissed completely.

First, if we were to adopt the earlier, as opposed to later, definitions of GLT (those that encompass gametes rather than embryos) then approaches such as PNT could be said to fall outside GLTs scope. PNT may therefore instead be 'somatic' because it is applied at an early stage of embryonic development. However, later GLT definitions that do include pre-embryos and embryos would run counter to this.

A second reason, as mentioned earlier, is that the inheritance of mitochondria is matrilineal. Only females born of an altered oocyte or embryo will pass their substituted mitochondria on to their children; and of

that second generation, again only females will pass them on. As such, if a male child is born with an altered mitochondrial genome, then no further generations are likely to inherit this change. Depending on the biological sex and reproductive outcomes of those born of this technology, replaced mitochondria may or may not be passed on. MTT that gives rise to male offspring may instead be a type of gene therapy that sits between somatic and germ-line. A change is made that affects every cell of the recipient, but will be very unlikely to be passed on to that individual's children.

It therefore appears that MTT does not easily fit a definition of somatic gene therapy, or would at least be a distinct form of somatic therapy. Therefore, we shall focus on whether MTTs are a form of GLT, as many have suggested or assumed.[66]

[66] e.g. Nuffield Council on Bioethics, op. cit. note 26; Rubenstein et al. op. cit. note 14; National Academies of Sciences, Engineering and Medicine, op. cit. note 52, Chapter 3, p. 8 (though note that they restrict their categorisation to female recipients only); F. Baylis. The ethics of creating children with three genetic parents. *Reprod Biomed Online* 2013; 26: 531-534; M. Darnovsky. A slippery slope to human germline modification. *Nature* 2013; 499: 127; Thorburn, et al., op. cit. note 22 (regarding ooplasmic transplantation; they claim it is germline modification but not gene therapy); Reddy, et al., op. cit. note 16; Tachibana, et al., op. cit. note 28; D.S. Kyriakouli, et al. Progress and prospects: gene therapy for mitochondrial DNA disease. *Gene Ther* 2008; 15: 1017-1023; Adams, op. cit. note 6; and E.Y. Adashi and I.G. Cohen. Going germline: mitochondrial replacement as a guide to genome editing. *Cell* 2016; 164: 832-835.

Given that the target in most MTTs is extra-nuclear, they will not be GLT if we take GLT to be synonymous with changes to nuclear DNA only. But if we accept that the target for change is beside the point and adopt a broad definition of GLT/IGM that encompasses any change to the genome of a germ cell, then MTTs may begin to look more like a germ-line intervention. Applying pertinent elements of IGM and HGLGM, MTTs are, prima facie at least: a form of modification; that acts on the genome; which are biomedically focused; are aimed at restoring (or perhaps enhancing) function and are undertaken intentionally.

However, as we will discuss further in Part V, at the very least this suggests that classifying MTTs does not appear to straightforwardly fall within existing (albeit contested) classifications. MTTs depart from predominant conceptions of IGM/HGLGM in two important ways: they are inherited only conditionally and may not always lead to a novel genome.

This leads us to the third option of our classificatory approach, which involves questioning whether the properties of MTTs should matter ethically, to use these concerns to guide classification. This means that rather than focus on the nature or type of an intervention, we look at its purpose and possible effects or consider their moral concern.[67]

[67] J.A. Robertson. Oocyte cytoplasm transfers and the ethics of germ-line intervention. *J Law Med Ethics*. 1998; 26: 179, 211-220.

IV. ETHICAL CONCERNS AND CLASSIFICATION

Interplay between classificatory status and ethical concern is a hallmark of debates over genome modification. Early demarcations between germ-line and somatic interventions focused on potential risk implications for future generations that might arise from altering the germ-line.[68] Subsequently, this has meant that any technological intervention classed as a GLT/IGM/HGLGT in humans has generally been deemed to be ethically problematic and, as such, prohibited.[69] By re-considering the classificatory status of MTTs in terms of the ethically relevant concerns arising, any association between MTTs and the inheritable interventions discussed above invites an exploration of the *grounds* for justifying such interventions, rather than simply accepting that they should be prohibited. However, we need to consider what ethically relevant issues for classification arise from MTTs before any such association can be made. Even if these do mirror those of traditional GLTs, we may still ask whether they generate the same intractable problems in this context.

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[68] F. Baylis & J.S. Robert. 2006. Radical rupture: exploring biological sequelae of volitional inheritable genetic modification. In *The Ethics of Inheritable Genetic Modification: A Dividing Line?* J.E.J. Rasko, et al., eds. Cambridge: Cambridge University Press: 131-148: 131; and The President's Council on Bioethics. 2003. Beyond Therapy: Biotechnology and the Pursuit of Happiness. United States: Executive Office of the President. Available at: https://repository.library.georgetown.edu/handle/10822/559341 [Accessed 6 Jan 2016].

[69] European Medical Research Councils, op. cit. note 2; UNESCO, op. cit. note 2; Council of Europe, op. cit. note 2.

Ethically relevant issues for classificatory concerns for MTTs cluster around several topic areas:[70]

(1) whether an intervention would provide treatment for some sort of identifiable medical condition, or whether it would constitute some other form of medical intervention;
(2) whether the intervention would be identity-affecting; and
(3) concerns about future generations;

MTTs and the treatment-enhancement distinction

Some early publications discussing gene therapy used the goal of the intervention – whether to cure or to enhance – as an indication of the permissibility of the approach.[71] Although the primary question so far has focused on the kind of intervention MTTs might be, concern has also been raised as to the possibility of it potentially being used for (currently impermissible) enhancement purposes.[72] From the perspective of classification, this would mean that MTTs might fall outside the scope of gene therapy on the grounds that they may not be a *therapy*, but an enhancement.

[70] This is not to say that MTTs don't give rise to broad concerns of safety, harm, and risk, only that the major classificatory concerns arise predominantly around these areas. For a wider range of ethical concerns associated with MTTs, e.g. Nuffield Council on Bioethics, op. cit. note 26; Bredenoord & Braude, op. cit. note 64; and Baylis, op. cit. note 66.

[71] e.g. Anderson, op. cit. note 3434.

[72] Baylis, op. cit. note 66. The definitions of gene therapy in Part III also refer to correcting defects or treating disease.

Such uses of interventions designed with the intention of being used as treatments, but which could also be used to enhance, is a long-standing problem; not least because the distinction between treatment and enhancement is a difficult one to make.[73] This difficulty is partly caused by a lack of conceptual clarity as to when an intervention is a treatment or an enhancement – they exist on a continuum.[74] Additionally, using this distinction to determine permissible and impermissible uses of a technology begs the question as to whether a clear conceptual distinction can be drawn in the first place.

Although a clear distinction between what constitutes a treatment or an enhancement may be difficult to establish, there will still be relatively clear-cut cases. If uses of MTT can clearly be shown to be treatment then, even if enhancement uses are possible in the future, it would strongly

[73] e.g. A. Buchanan. 2011. *Beyond Humanity? The Ethics of Biomedical Enhancement*. Oxford and New York: Oxford University Press; J. Savulescu, et al. eds. 2011. *Enhancing Human Capacities*. New York: Wiley-Blackwell; F.M. Kamm. Is there a problem with enhancement? *Am J Bioeth* 2005; 5: 5-14; and P.H. Schwartz. Defending the distinction between treatment and enhancement. *American Journal of Bioethics* 2005; 5: 17-19.

[74] Difficulties over accurately drawing the therapy/enhancement distinction have been used by Resnik & Langer, op. cit. note 29, as an argument for the inadequacy of the use of the term 'human germline *gene therapy*' (emphasis added) on the grounds that it cannot capture all such distinctions surrounding procedures intended to alter the human germ-line genome.

indicate that MTTs should be classed as therapies. The reason this distinction need only satisfy central cases of MTTs being classed as 'treatments' is that many biotechnological interventions that would have an application as enhancements will have been developed as having some sort of therapeutic purpose.[75] Accordingly, the technology would have been developed and used based on those therapeutic benefits, rather than a need to justify it as an enhancement. Hence, while there might be benefits to mitochondrial replacement that could be achieved for those without an identifiable mitochondrial disorder,[76] there remain clear-cut therapeutic applications of MTT. It is these that should form the core for classification.

However, this places a large part of the classificatory burden onto whether MTT actually achieves the intended goal of being a therapeutic treatment. Addressing whether MTTs can be considered as therapies at all raises a new classificatory concern that is not based on the distinction between treatment and enhancement but rather a consideration of who the subject of the MTT intervention is and whether they can be said to be receiving a

[75] That biomedical interventions have both therapeutic and enhancement uses is widely recognized and has led to concern over how to demarcate the two. See, for example: M.J. Mehlman. How Will We Regulate Genetic Enhancement? *Wake Forest L Rev* 1999; 34: 671– 617.; Buchanan, op. cit. note 73; The President's Council on Bioethics, op. cit. note 68; and Kamm, op. cit. note 73.

[76] For example: augmentation of energy production, or reducing the likelihood of obesity or risk of diabetes.

treatment. Such a consideration involves issues of identity and how the method of MTT used can lead to a distinction between treatment and reproductive selective choice.[77]

Identity Concerns in MTTs

Issues of identity underpin concern as to whether or not there is an *identifiable individual* who can be said to receive MTT. This, in turn, may be pivotal as to whether MTTs can be classified as a *treatment* (therapy) at all. The concern arises because of the individually oriented way that gene therapy is defined.[78] If such definitions are sound, then anything that does not treat a specific individual may not be classifiable as gene therapy.

Questions of identity inevitably rely upon metaphysical theory. Engaging with contentious views as to the nature and origins of persons may not seem an appealing or relevant basis in which to ground MTT ethics and policy, particularly given there may be substantial implications as to the treatment or welfare of future individuals, or where disagreement over metaphysical positions might be deemed too abstract to shape matters of

[77] Reproductive selective choice concerns prospective parents choosing reproductive methods that may lead to the creation of different possible future children. Parents can choose the child whom they consider will have the best quality of life. See S. Wilkinson. 2010. *Choosing Tomorrow's Children*. Oxford: Oxford University Press.; and A. Wrigley, et al. Mitochondrial Replacement: Ethics and Identity. *Bioethics* 2015; 29: 631-638.

[78] See Part III above.

such practical importance to people's lives.[79] However, questions like this have played a major role in debates surrounding harms and benefits for future generations. Moreover, some issues - particularly those surrounding the margins of life - will inevitably give rise to concerns that are metaphysical in nature.[80]

One of the most compelling and widely cited accounts of identity is given by Parfit.[81] Not only can Parfit's arguments be used to raise questions about whether an individual can be harmed or benefit by choices concerning their originating genetic constitution – which can include MTTs – it can also be used to raise an interesting classificatory concern based on whether or not there is an identifiable individual who can be said to be the

[79] e.g. Lewens, op. cit. note 5. Lewens raises concerns as to the emphasis placed on identity and origin.

[80] e.g. D. Parfit. 1984. *Reasons and Persons*. Oxford: Oxford University Press; J. Feinberg. Wrongful life and the counterfactual element in harming. *Soc Philos Policy* 1987; 4: 145-178; M. Hanser. Harming future people. *Philos Public Aff* 1990; 19: 47-70; D. Velleman. Persons in prospect. *Philos Public Aff* 2008; 36: 221-288; A. Wrigley. Genetic selection and modal harms. *Monist* 2006; 89: 505-525; A. Wrigley. Harm to future persons: non-identity problems and counterpart solutions. *Ethical Theory Moral Pract* 2012; 15 175-190; and Wrigley et al., op. cit. note 77.

[81] Parfit, Ibid.

subject of the MTT. Parfit provides an account of identity in terms of our originating gametes.[82] According to this 'Origins View':

> …each person has this distinctive necessary property: that of having grown from the particular pair of cells from which this person in fact grew.[83]

This means that anyone's existence is dependent upon a particular egg being fertilized by a particular sperm. If a different sperm or egg had been involved, then a numerically different person would have existed instead. This underpins the Non-Identity Problem; that a person cannot have been made worse (or better) off than they otherwise would have been through pre-conception actions that alter the fertilizing gametes involved because they would not have existed at all if those pre-conception actions had been

[82] This is an account of our numerical identity – whether we have the same or different object – and is distinguished from other senses of identity, such as qualitative, personal, or social identity.

[83] Parfit, op. cit. note 80, p. 352. This 'Origins View' position is derived from S. Kripke. 1980. *Naming and Necessity*. Oxford: Blackwell. Parfit in fact held a somewhat weaker version of this, called the 'Time Dependence Claim', which has the slightly more pragmatic claim to conception within a certain time-limit. This is a less contentious position but one that would pose problems in its application to reproductive technologies, where gametes can be stored for years, as opposed to natural conception. The Origins View, although widely used in discussions of genetics and reproductive technologies, is not without critics. See: D. Lewis. 1986. *On the Plurality of Worlds*. Oxford: Blackwell and P. Mackie. 2006. *How Things Might Have Been: Individuals, Kinds, and Essential Properties*. Oxford: Oxford University Press.

any different. Such changes to the originating sperm or egg involved in conception would have resulted in an entirely different person existing instead.

The question as to whether MTTs affect identity in a way that is subject to the Non-Identity Problem is dependent upon the particular MTT. In MST, the intervention is carried out prior to fertilization; when no individual could yet be said to be determined. In PNT, the pronuclei transfer is performed after fertilization; when numerical identity has already been established. This would indicate that the Non-Identity Problem could apply to MST, if, for example, a different sperm fertilised the egg than if the maternal gamete had not undergone manipulation.[84] There may also be further concerns as to whether the changing of the mitochondrial genome can alter the genetic identity of the oocyte to the point where it is considered a different egg than if MST had not taken place.[85] Accordingly,

[84] It should be noted that this is not an absolute necessity – the same sperm that would have fertilised the egg if MST had not taken place could, conceivably, have done so with the MST process. This is extremely unlikely as a random possibility, but may be more likely if sperm were pre-selected for fertilization and would be used regardless of whether the MST process was employed. This means that the Non-Identity Problem may not apply in all possible cases of MST, but if mitochondria do alter genetic identity then it will apply regardless of whether the same or a different sperm is used to fertilise the modified oocyte.

[85] The issue of whether altering the mtDNA of an oocyte in this way is sufficient to mean that an entirely different egg has been created than would otherwise have been used in

such a method could not harm the resulting child (unless they are deemed to have a life not worth living) because a numerically different individual would have been born if MST had not been used.

If MST could not be said to harm the resulting child, it also could not benefit them. Given existing claims that gene therapies must benefit *individuals*, MST would therefore not be a therapy.[86] The determination of genetic status has been made prior to the conception of the resulting child. Any other choice or selection would have resulted in different gametes being used[87] and hence a different child being conceived.[88] There is, therefore, no individual patient who has had their genetic defects

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conception is beyond the scope of this paper. The role of mtDNA in this regard is unclear. However, the concern that such radical manipulation of an egg may result in its destruction and replacement by a new egg may have some support based on an essentialist 'organism view', as implied by Liao: S.M. Liao. The organism view defended. *Monist* 2006; 89: 334-350. If this were the case, then it may also have further implications as to whether a similar argument can be made for the zygote in the case of PNT.

[86] As implied by Frankel & Hagen, op. cit. note 32, p. 8-9; and Nuffield Council on Bioethics, op. cit. note 26, p. 57.

[87] For example, an oocyte that had not undergone MST; or a donor oocyte.

[88] In making this point, we are assuming that mitochondria are relevant to numeric identity. However, this point is not settled; as discussed above.

'treated'.[89] There is simply a person born who is very unlikely to have (or develop) a mitochondrial condition.

As PNT occurs *after* fertilization, this would alter the genome of an already existing individual.[90] The Non-Identity Problem would not arise, as it would be possible to consider *that particular child's* welfare had they not had PNT. It also means that PNT could potentially be classifiable as a beneficial treatment to an identifiable individual who would otherwise have had a debilitating mitochondrial disease. This form of MTT could therefore be defined as a gene therapy.

[89] It is possible by definition to widen the scope of therapeutic target such that, for example, one may claim that the individual being treated is the mother using the technique to 'treat' her condition of 'being unable to have children who would not pass on mitochondrial disease to their future children', such as has been suggested by as Frankel & Hagen, op. cit. note 32. However, there would have to be some reasonable consensus agreement in medicine that such expanded definitions really were instances of a recognisable condition before such a move could be considered as potentially influencing the classification of MTTs.

[90] Although outside the scope of this paper, the previously mentioned possibility in note 85 of whether the Non-Identity Problem applies in the case of PNT too would be relevant here.

As only PNT is readily classifiable as a gene therapy, we are left with the question of how to classify MST. [91] One consideration is that MST might be considered as a 'reproductive technology' rather than a gene therapy, as currently understood, and therefore might be better classified as offering reproductive selective choice rather than treatment. Or, MST may fit within the description of IGM or HGLGM. Regardless, MST would allow a woman or couple to exercise a certain aspect of choice over their future - but not yet existent - children; namely the choice to have a child who is both genetically related to its mother and unlikely to have or develop a mitochondrial condition.

This classificatory distinction may also have ethical implications for the use of MTTs depending upon attitudes towards the goals of medicine, such as whether *treatment* of individuals is more important than allowing parents to exercise reproductive selective choice.[92] Yet we are nevertheless left in something of a strange position with MTTs, in that the way in which they are carried out can be relevant to their classificatory status as a treatment rather than such a classification simply being premised on a perceived goal

[91] We use the term 'readily classifiable' here as we have recognised the potential for rejecting the Non-Identity Problem as well as the possibility of widening the scope of 'therapy'. However, both of these exceptions are sufficiently tenuous so as not to directly shape the classificatory argument.

[92] For further discussion of the identity issues raised and of their ethical implications, see: Wrigley et al., op. cit. note77.

of eliminating mitochondrial disease. What does emerge, however, is that whether a MTT is a *therapy* or an exercise of *reproductive selective choice*, they can all be considered as conditionally inheritable genomic modifications.[93]

Ethics and the impact of MTTs on future generations

As we have discussed, anything with the potential to lead to inheritable change gives rise to concerns about unforeseen consequences for future generations.[94] Recognising the matrilineal inheritance of most MTTs, these possible consequences may be over-emphasised given that transmission will cease if a male child is born. The 'conditional inheritability' of MTTs mitigates concerns about the unbounded effects of altering a genome even though it does not entirely remove the possibility. While this is simply a reining-in of a statistical chance, this reduction in the likelihood of transmission means it is reasonable to question whether precautionary fears about harms to future generations should be given such weight in assessing the ethical implications of MTTs.[95]

[93] We discuss this further in Part V below.

[94] K.R. Smith. Gene Therapy: Theoretical And Bioethical Concepts. *Arch Med Res* 2003; 34: 247-268; and Chadwick, op. cit. note 17**.**

[95] One response to this is to require all children born using MTT to be male in order to prevent transmission, such as has been suggested elsewhere: National Academies of Sciences, Engineering and Medicine, op. cit. note 52; Appleby, op. cit. note 60; Bredenoord et al, op. cit. note 60. This position would largely eliminate concerns about risks to future generations, but require additional intervention alongside MTT to enable

V. CLASSIFYING MTTS AS CONDITIONALLY INHERITABLE GENOMIC MODIFICATION (CIGM)

MTTs do not appear to fit directly into an established traditional (narrow) classificatory category of somatic or germ-line therapies. Utilizing broader classifications, such as IGM or HGLGM, also seems to fail to adequately provide a means of classifying MTTs; at least insofar as the fact that it groups MTTs with interventions that they depart from in several significant ways. Looking at key ethical issues that surround MTTs also raises problems for classification: the treatment/enhancement distinction is rebuttable; not all MTTs will target individuals; and concerns for future generations can be mitigated by their conditional inheritability. To consider an alternative classification would seem both reasonable and, at least partially, follow what Frankel and Hagen imply when they claim that: 'there may still be ethical distinctions between types of germ-line modification.'[96]

As narrow-scope (approach (a) in Section I) attempts at classification fail to adequately capture all the features of MTTs, and with broader scope (b) and ethics-driven (c) classifications also raising problems, we propose that MTTs should be classified using a novel account of genomic modification;

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sex selection. This would also not necessarily change the classification for MTT as it would be an additional intervention. However, the full scope of such a policy decision and its implications is outside the scope of this paper.

[96] Frankel & Hagen, op. cit. note 32, p. 6.

one that recognises that MTTs have some (but not all) properties of classically defined somatic and germ-line therapies or modifications, but also that they demonstrate conditional characteristics of inheritability. They form a (non-exclusive) sub-category of inheritable modification, which we call 'Conditionally Inheritable Genomic Modification' (CIGM).

CIGM as a sub-category of inheritable modification differs from the 'standard' account of inheritable genetic modifications due to them being '*conditionally* inheritable', which recognises matrilineal inheritance, bottleneck effects and unpredictability in mitochondrial segregation.[97] We have also adopted Resnik and Langer's use of 'germline' rather than 'genetic' modification to avoid problems of MTTs targeting organelles rather than genes. However CIGM departs from HGLGM in that MTTs will not always give rise to a novel genome.[98] It is important to note that CIGM is a sub-category of genomic modification that will include MTTs (and their various features discussed in Part III), but that it also could encompass techniques other than MTTs because it is neutral with regard to the *target*

[97] In the sense that MTTs do not rely on future generations having modified mitochondria, as they are only inheritable under limited conditions; discussed in Part III. Bredenoord et al. have made a similar claim regarding MTTs as a particular class of 'germ-line genetic modification': Bredenoord, et al., op. cit. 27; as have Frankel & Hagen, op. cit. note 32, p. 6; Thorburn et al., op. cit. note 22; and the Nuffield Council on Bioethics, op. cit. note 26: 58-9. However Bredenoord et al's categorisation relies on the invasiveness of the intervention, whereas we draw on its conditional inheritability.

[98] As discussed in Part III above; specifically note 62 and the accompanying text.

of the modification. This would also allow MTTs to be classified as genomic modifications without the need for a therapeutic distinction being made – both MST and PNT could be classified as CIGM. Yet it also excludes those broader interventions that might be seen to change the human germline without altering the genome, such as PGD or gamete donation, thereby avoiding category inflation by excluding a range of widely recognised reproductive interventions.

Yet while CIGM is non-exclusive to MTTs, it may not encompass *all* MTTs. For example, Smeets' scenario involving donated oocytes with mtDNA matched to the intending mother may not strictly be a 'modification'[99] unless we were to define modification as encompassing methods of directed evolution as well as intention to change genomic inheritability.[100] CIGM also differs from the classification reached by the US National Academy of Science and Engineering in Medicine; who claim that only MTTs leading to female offspring would constitute an IGM, not those that

[99] As the genetic complement of the resulting child would match that in the mother. See also note 62.

[100] However, pre-implantation genetic diagnosis to avoid the birth of a child with a mitochondrial condition may then also be defined as a CIGM. This may mean that we need to treat PGD the same as some MTTs, or that the particular form of MTT that Smeets (op. cit., note 59) is referring to is different in kind from other MTTs. Such an analysis is beyond the scope of this paper.

give rise to males.[101] The Academy appears to base its classification of the outcome of the intervention; whereas we have based our classification on the properties and inheritability of the intervention itself.

VI. CONCLUSION

We have developed a new classification to encompass MTTs, called 'conditionally inheritable genomic modifications' (CIGM); a new sub-category of genomic modification. CIGM fits between the narrow and broad approaches we described in Part I and accounts for the scientific and ethical distinctions MTTs give rise to. It is not a category solely for MTTs but it allows them to be classified in a manner that avoids many of the concerns that arise from attempting to classify them through previously established categories.

There remain wider implications for adopting such a category, however. Although our classification of MTTs as CIGMs might indicate that their automatic prohibition as germ-line therapies is not warranted, it would not settle the question surrounding ethical concerns retained from other debates about genetic modification that don't depend on classification. [102]

[101] National Academies of Sciences, Engineering, and Medicine, op. cit. note 52, Chapter 3, p. 8.

[102] We are here taking the "automatic prohibition" of germ-line interventions as being derived from existing international policy, which we interpret as indicating that germ-line modification should be prohibited. However, our point is that other ethical issues in MTTs

For example, we would still require sufficient knowledge of the effects of altering an oocyte's mitochondria to make judgements about potential harms to future generations, and the standing question as to whether the therapeutic benefits outweigh potential harms would still need to be addressed.

Moreover, in suggesting a change to the established categories of classification, we are aware that we might simply be encouraging an over-expansion of classifications. In this case, however, we think it warranted. Although utilising a known or existing classification might have certain advantages due to its placement within a category with established ethical positions and regulatory instruments, this would seem to be 'shoe-horning' MTTs to a category they do not readily fit for the sake of taxonomic parsimony.

Adopting CIGM will also have additional implications such as: 'Does CIGM need specific regulations?' and 'Does it have ethical issues all of its own?' But asking these questions will address concerns that we would be encouraging re-classification simply as a means of avoiding ethical scrutiny of MTTs. It might even go further by actually preventing ethical laxity through blocking the presumption that no new ethical issues arise from classifying something within an already established category.

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will remain relevant regardless of its classification. See citations in note 2 for the most notable internationally recognised prohibitions on germ-line modifications.

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