Preventing mitochondrial disorders through nuclear transfer techniques: social and ethical issues (preliminary and incomplete)

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1. Introduction

The emergence of nuclear transfer (NT) techniques aimed at preventing the transmission of inherited mitochondrial disorders has recently become the subject of much interest, especially in the UK where a research team in Newcastle has successfully applied these techniques to human embryos¹. The development of these techniques arouses both hope and concern regarding the possibility to permit them for treatment. This issue nevertheless raises several fundamental ethical questions, in particular whether or not NT techniques should be regarded as germ-line therapy. Germ-line modifications generally refer to genetic modifications of the gametes or the early embryo which will be passed on to the subsequent generations⁶, unlike gene therapies which affect only the patient concerned. Since germ-line modifications are currently prohibited, the scientific and ethical categorization of nuclear transfer techniques is crucial for determining their social acceptability and legality. More broadly, this issue also puts into question and challenges many important ethical references and concepts.

In this paper², I will examine some of the issues raised by the NT techniques with respect to germ-line modifications, in particular the criteria considered to define germ-line therapies and the principles raised to ascertain their ethical acceptability. After briefly describing what mitochondrial disorders and nuclear transfer techniques consist of, I will examine the two main conceptual positions, i.e. either to consider NT techniques as germ-line therapy or the contrary. In both cases, I will first develop the arguments which have been put forward by some bioethicists to justify such positions. I will then look at the different principles that could justify the decision to legally prohibit or to permit NT techniques and the further questions that could arise for each option. To conclude, I will point out some broader questions that the germ-line therapy issue opens up while replacing NT techniques in a broader context.

¹ Craven et al., “Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease.”
² This analysis is part of a broader research on the social and bioethical issues of nuclear transfer techniques for mitochondrial disorders. Please, be aware that this research is just at its onset. The research aims to empirically study the views and experiences of genetic counsellors and patients affected by mitochondrial disorders with respect to reproductive choices. This would enable the conception of healthy biological children, whose DNA would be. The research examines current ambivalences and concerns regarding existing and new biotechnologies, as well as their broader impacts.
2. **Background**

Mitochondrial disorders result from mutations of the mitochondrial DNA present in the cell cytoplasm or from mutations of the nuclear DNA. The current paper project focuses only on the former cases, which are maternally-inherited. Often under-diagnosed or misdiagnosed, these disorders affect approximately one person in every 5000 to 6500. Mitochondrial mutations can cause severe diseases and various body dysfunctions through defects in the energy production in cells, such as dementia, blindness, or myopathy. There is no known curative treatment for these disorders. Therefore, a woman who has been diagnosed with MT disorders and her possible partner face much uncertainty if they want to have children because it is very difficult to predict if their future child will develop disorders and at which stage of life. Women carriers currently have several alternatives in their family planning: naturally conceiving a child with the risk of transmitting the disorder, adopting a child, turning to egg donation, or using prenatal or preimplantation genetic diagnosis (PGD). However, while abortion or PGD may help reduce the transmission of risk, there remains a significant amount of unpredictability remains. Moreover, these medical options necessitate embryo selection or abortion. Under such conditions, a woman with a MT disorder may face difficult dilemmas in their family planning given that men and women with other types of genetic disorders have been found to report a great deal of uncertainty.

A new set of reproductive choices is now emerging from research underway in the UK and elsewhere to develop new cell reconstruction techniques that aim to prevent the transmission of MT disorders to biological offspring. They consist of transferring the (pro)nuclear DNA of the affected mother’s oocyte or embryo into a healthy enucleated donor egg or early embryo. This genetic intervention can thus be applied before fertilization, through techniques such as ‘maternal spindle transfer’ (MST), or after it, by ‘pronuclear transfer’ (PNT). The striking novelty is that the conceived child will inherit DNA from three individuals, not only the nuclear genome from both intending parents (99.9%) but also, albeit to a much lesser extent (0.1%), the mitochondrial DNA from the egg donor.

MST and PNT techniques are still at an experimental stage and are not permitted for use in treatment under UK legislation. However, a licence has been granted by the Human Fertilisation and Embryology Authority (HFEA) in 2005 to the Newcastle Fertility Centre to carry out research investigating PNT using human embryos. According to the Nuffield Council on Bioethics, “it [is] foreseeable that in the relatively near future Parliament could debate the approval of regulation-making powers in the Human Fertilisation and Embryology Act 1990 (as amended) to enable the techniques to be as offered as treatments.” Although the genetic changes produced by these techniques may seem minor or superficial in quantitative terms, the development of these techniques, whose first results seem so promising, nevertheless raises various challenging legal, bioethical, and social issues. Both the Nuffield Council on Bioethics (NCB) and the HFEA have recently called for detailed

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3 Bredenoord et al., “Dealing with Uncertainties: Ethics of Prenatal Diagnosis and Preimplantation Genetic Diagnosis to Prevent Mitochondrial Disorders.”

4 Menon et al., “Views of BRCA Gene Mutation Carriers on Preimplantation Genetic Diagnosis as a Reproductive Option for Hereditary Breast and Ovarian Cancer.”
research into those issues to be undertaken and for a public consultancy to be launched. The NCB report was published in June 2012 and the HFEA report will be released in March 2013.

3. Analysis
Since their inception, NT techniques have been the subject of much debate and a key issue relative to these techniques is how to conceptualise them with respect to germ-line modifications. NT techniques do indeed modify mitochondrial genome by replacing the intending mother’s mutated mitochondrial DNA by that of the egg donor. The donor’s mitochondria DNA will then passed on to the subsequent generations along maternal line. Ongoing conceptions on that matter are strongly divergent and have various ethical and legal implications. As shown below, one of the main elements of divergence is the relevant criteria to ascertain the conceptual status of these techniques: should the biological distinction between nuclear DNA and mitochondrial DNA be considered or rather the modification of the identity itself? Another crucial decision lies in allowing or prohibiting these techniques following such specific conceptions. What would then be the principles underlying such decisions and their logical ethical consequences?

a. NT techniques are germ-line therapy
   • Ethically unacceptable
A first reason that makes many people regard NT techniques as germ-line therapies is the fact that they involve genetic changes which will be transmitted over the generations. This means that not only the person conceived with these techniques will be affected by these techniques but the future generations will also incur some risks in terms of health and identity. As it is difficult to assess the possible short and long-term effects of these techniques without experimenting them on several generations, some argue that it is not reasonable to allow such techniques. This stance thus seems to pertain to the precautionary principle.

Apart from the techniques’ intergenerational effects, some people also consider NT techniques to be germ-line therapies because they would alter genetic inheritance. In this respect, it is important to note that genetic inheritance is conceived as a whole. As such, the genetic profile of the resulting offspring will in fact not be the same if their maternally inherited mitochondrial DNA has been replaced by that of an egg as if not. This argument is then used to present NT techniques as ethically unacceptable on the ground of the following principles which have previously been used to prohibit germ-line therapies:

1- the individual’s right to an open future: by not tampering his or her unique characteristics and genetic inheritance.

2- the preservation of the “social order”: by preventing human enhancements and the inequitable distribution of some genetic advantages.

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5 For more detail on these principles, see Munson and Davis, “Germ-line Gene Therapy and the Medical Imperative.”
3-the preservation of the “order of nature itself”: in particular by avoiding technological and medical interventions.

Finally, some protagonists acknowledge that modifications of the mitochondrial genome is different and not as problematic as modifications of nuclear genome but argue that allowing the former will inevitably lead to permit the latter in the future. It could also open the door to the acceptance of human enhancement. It is the argument of the slippery slope.

- Ethically acceptable

In the recent Nuffield Council on Bioethics’ (NCB) report on NT techniques, the Working Group spoke in favour of NT techniques as representing a form of germ-line therapy which modifies the mitochondrial genome and will be transmitted over the generations.\(^6\) In so doing, they follow the criteria previously put forward by A. Bredenoord. This bioethicist disagrees with making an ethically significant distinction between modification of the nuclear DNA and modification of the mitochondria DNA. Among other reasons, this distinction is problematic as some uncertainties remain\(^7\) regarding the biological functions of mitochondria and the nucleo-mitochondrial interactions.\(^9\) But more significantly, she argues that both affect the “qualitative identity” of the future person. Indeed, some aspects of the person conceived with NT techniques will definitely be different from what they would have been, should the techniques not have been used.\(^10\) Not only will the person’s mitochondrial genome be altered, even though in a minor way, but the person’s self-conception will also significantly differ from what his or her self-conception would have been as a person developing mitochondrial disorders. In addition, this person’s self-conception might be affected by knowing that s/he has been medically conceived with the donor’s genetic contribution.\(^11\)

According to the NCB Working Group, NT techniques can also been regarded as altering the “numerical identity” of the resulting offspring because “the inclusion of a donor’s mitochondrial genes and minimisation of the proportion of maternal mitochondrial genes could make such a very significant difference to the resulting person’s life that they could be said to make them ‘a different person’.”\(^12\) While the NCB Working Group therefore definitely considers NT techniques as germ-line therapies, they nonetheless add that “some changes to the mitochondrial genes have germline effects that are different from the germline effects of changes to nuclear genes. Differences include that PNT and MST are not intended or known to affect nuclear genes; they aim to make no changes to the donor’s mitochondrial; and only women born from these techniques would be able to pass the changes on to their

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\(^7\)Bonnicksen, “The Politics of Germline Therapy.”

\(^8\)Thorburn, Dahl, and Singh, “The Pros and Cons of Mitochondrial Manipulation in the Human Germ Line.”

\(^9\)Poulton et al., “Nuclear Transfer to Prevent Mitochondrial DNA Diseases.”

\(^10\)Ethics of nuclear transfer to prevent mitochondrial DNA disorders: revisiting the debate on germ-line modification and reproductive cloning.


\(^12\)Ibid., 55.
children”\textsuperscript{13}. This means that although germ-line modifications should primarily be defined with respect to their impacts on the future person’s identity, the Working Group believes that different types of germ-line modifications could be acknowledged according to the targeted genome, the nature of the genetic manipulation (replacement or specific modification), and their scope (impact on all resulting offspring or only part thereof). This stance leads the Working Group to imply that different types of legal regulation could also be required\textsuperscript{14}.

Acknowledging that NT techniques are qualitatively, and possibly numerically, identity-altering does not mean, according to Bredenoord and the NCB Working Group, these techniques are ethically unacceptable and should be prohibited. For the Working Group, the reason is that such effects are not specific to NT techniques. More importantly, the Working Group aligns itself with Bredenoord’s view that the significant criterion which should be taken into account to evaluate the moral acceptability of germ-line therapy is its effect on the resulting offspring’s right to an “open future”. This notion was developed by J. Feinberg to designate “the importance of not closing off the child’s future options, in order not to restrict his or her ability to author his or her own life”\textsuperscript{15}. In this respect, NT techniques do not harm the resulting child’s right to an “open future” according to Bredenoord. Indeed, it is rather the contrary as it will enable the child to avoid very serious disorders that would compromise their life and projects\textsuperscript{16}.

b. NT techniques are not germ-line therapy

- Ethically acceptable

Some experts, including several of the UK researchers who have developed NT techniques\textsuperscript{17}, do not regard these techniques as germ-line therapies. They argue that germ-line modifications initially referred to changes in the nuclear DNA, which is thought to determine all our personal characteristics. In that respect, PNT and MST techniques leave the nuclear DNA intact. According to these researchers, while there are different kinds of risks in modifying the nuclear genome because of its complexity, mitochondria DNA is much simpler and can be compared to the need to change a “battery” in the case of mitochondrial disorders. As for other protagonists, such as Dr Evan Harris MP\textsuperscript{18}, there is a significant distinction between the nuclear DNA and the mitochondrial DNA in terms of biological functions and composition.

For these various protagonists, the fact that NT techniques cannot be considered as germ-line therapy means that these techniques should not be treated as such and prohibited. This stance

\textsuperscript{13} Ibid., 58–59.
\textsuperscript{14} Nuffield Council on Bioethics, \textit{Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review}.
\textsuperscript{15} (to be completed)
\textsuperscript{16} Bredenoord et al., “Ethics of Modifying the Mitochondrial Genome.”
\textsuperscript{17} North East England Stem Cell Institute, “Briefing Paper on the Need to Protect the Future Possibility of Treating Mitochondrial Disease and Other Conditions by a Procedure That Involves Mitochondrial Transplantation.”
is in favour of permitting NT techniques for treatment, while maintaining the ban on germ-line therapy strictly defined as modifications of the nuclear DNA.

- **Ethically unacceptable**

- impossibility to obtain the consent of the first directly affected by these techniques, i.e. the children conceived with NT techniques.

- the resources needed for the development of these techniques which target very few people and to render them available to the patients, although other alternatives are already available (egg donation, PGD, PND).

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Discussion:

These techniques thus bring into question the complex issue of what defines a germ-line modification and, moreover, how these modifications may alter the essential characteristics that many believe determine our identity\(^{19}\). Ultimately, they problematize the current ban on germ-line therapies.

References


\(^{19}\)Bredenoord, Pennings, and De Wert, “Ooplasmic and Nuclear Transfer to Prevent Mitochondrial DNA Disorders: Conceptual and Normative Issues.”

