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From Embryo Research to Therapy

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"Embryo and Developmental Research" Group

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A child of one's own

It was Aristotle who said that human beings, like all living beings, have "a natural desire to leave behind them an image of themselves".[1] A desire that he considered to be the natural foundation of the conjugal union – a natural foundation to which many social foundations are, of course, added. While our conception of what is natural has changed considerably since the age of Aristotle, this desire remains visible in our modern societies – with assisted reproductive technology (ART) being evidence of this. The majority of couples want children, children of their own[2], meaning that in the event of infertility, many of those affected turn to medicine rather than adoption[3] to help them overcome the obstacles thrown in their path by nature – paradoxically opposing a desire that in itself is partially natural.

For a long time, ART was limited to artificial insemination, with donor or partner sperm. But with the birth of Louise Brown in 1978, the technology has undergone an extraordinary expansion, considerably opening up the realm of possibilities. In order to develop *in vitro* fertilization (IVF), research on human embryos was necessary. Research that continues to remain necessary if we are to improve and evaluate these techniques, not just for the benefit of infertile individuals but also that of children. According to a 2016 study conducted on children born using ART, they presented a more or less high risk of developmental disorders at 5 years of age, depending on the culture medium used for the IVF.[4] It is therefore necessary to intensify research in this area for the development of even safer media.

1. Aristote, *La Politique*, Paris, Vrin, 1970, p. 25.
2. The parents also wish to *procreate*, with all that it implies in terms of personal investment, including for gestation and delivery.
3. If they do not turn to adoption, it is also for reasons of feasibility. While around 800 children are declared adoptable each year in France, around 25,000 couples or individuals are estimated to be approved, that is to say they have gone through all the relevant processes.
4. Céline Bouillon & al., Does Embryo Culture Medium Influence the Health and Development of Children Born after In Vitro Fertilization?, *Plos One*, 2016, DOI:10.1371/journal.pone.0150857.

Treat not destroy

Parents do not just wish to have a child but one in good health. When a couple is known to have a disease of genetic or chromosomal origin, it has since the 1990s been possible to diagnose it in embryos created from its gametes prior to implantation and to avoid transferring affected embryos to the uterus. Therefore, once the serious disease in question is detected in an embryo using pre-implantation genetic diagnosis (PGD), the embryo is not transferred to the uterus. In parallel, and for a long time now, many parents decide to terminate the pregnancy should prenatal diagnosis detect a chromosome abnormality or severe malformation syndrome in the gestating fetus. As far as embryos are concerned, we often refer to "screening", a term that carries an implicit negative moral evaluation. There are several reasons for this, which are themselves subjects for debate, but one is that the embryo is then discarded: because of some of its characteristics, it is destroyed or donated to research. Indeed, the embryo is not considered a person under French law. Consequently, the French National Consultative Ethics Committee (CCNE) has defined it as a "potential human person" (PHP),[5] thereby emphasizing that it is not a person. On a philosophical level, we could say that all French citizens are *potential* Presidents of the Republic, which means that they are clearly *not* Presidents of the Republic. However, destroying an embryo that is liable to become a human being is never an optimal solution and can cause suffering for the couple in question. All the more so if the embryos obtained are all affected, which can unfortunately sometimes happen.

A better solution would, of course, be to treat or even cure them. A certain number of current studies are heading in this direction, and the benefits they suggest form strong justification for the research performed on embryos that can in some way be said to be for their benefit. This assertion appears paradoxical, given that in order to develop embryo therapies, invasive studies are required in which some lead to the destruction of embryos. But we must not lose sight of the fact that it is for the benefit of other embryos that could lead to the birth of healthy children who, for their part, are people. It must be emphasized here that treating an embryo does not make it a person: all living beings are liable to receive treatment, but few living beings are people. Furthermore, the fact that the embryo is a particularly vulnerable living being does not make it a person either, although as a potential person it requires solicitude and respect.[6]

In this way, research on embryos can benefit the embryos themselves, *directly* and *indirectly*.[7] It *indirectly* benefits future embryos and it *directly* benefits the embryo itself when

5. CCNE, Opinion on sampling of dead human embryonic and fetal tissue for therapeutic, diagnostic, and scientific purposes (Opinion no. 1), May 22, 1984.
6. To the question asked by Pierre Jouannet: "Does comparing a days-old embryo to a patient imply that it is a person? " (L'embryon sujet: patient d'une médecine de l'embryon ? L'embryon objet: quelle recherche et pour qui ?, in Pierre Jouannet and Catherine Paley-Vincent, *L'embryon, le fœtus et l'enfant*, Paris, Eska, 2009, p. 78), the answer, of course, is no. "Being a patient" does not imply "being a person".
7. Pierre Jouannet, *ibid*., p. 83.

it can be subsequently transferred to the uterus for gestation as provided for by law since 2016 (French Public Health Code, L 2151-5), which was confirmed by the French Constitutional Council considering that these clinical trials do not lead to the embryo being placed at a risk out of proportion to the expected benefit.[8]

Several therapeutic approaches in favor of the embryo are currently in development and are subject to much research. At least two of them have already been used in the clinical setting with the aim of bringing a child into the world – namely *mitochondrial replacement therapy* and *treatment of triploidy*, which are the subject of this document.

Before examining them in more detail, it must be noted that four scenarios must in general be distinguished:

1. *Embryo screening*, when it is decided to not transfer an embryo and to destroy it because it is considered abnormal (for example, it is triploid) or unsuitable for development (for example, it has morphological abnormalities). Screening is also performed when, in an embryonic cohort, it is chosen to transfer some embryos rather than others, because their characteristics offer better chances of pregnancy.

2. *Embryo destruction*, which primarily concerns embryos with diseases, and sometimes also normal embryos to fulfill the decision of people not wishing to continue to store frozen embryos as part of a parental project.

3. *Embryo treatment*, which concerns embryos with treatable diseases.

4. *Embryo reconstitution* from multiple embryo sources.

Restoration of diploidy is an actual treatment (3), whereas mitochondrial replacement therapy still involves the reconstitution of an embryo (4).[9]

One question that immediately arises when it comes to treating embryos is whether germline gene therapy is involved. Given that the latter is forbidden and that these two approaches have already been used, it is evident that it had not been judged in this way. This is because they do not involve modifying the structure of the genes themselves, whether at nuclear (nuclear genes) or mitochondrial level, but this could be contested if, like certain authors, we consider that “the goal of germ-line gene therapy [consists of introducing] transgenic cells into the germ line as well as into the somatic cell population. Not only should this therapy achieve a cure of the person treated, but some gametes could also carry the corrected genotype”.[10]

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8. The French Constitutional Council considers that “subjecting to clinical trials techniques in development that are intended to improve the efficacy of ART methods or to prevent or treat embryo diseases” is necessary and “that these clinical trials, conducted for the benefit of the embryo itself or for ART research, do not lead to the embryo being placed at a risk out of proportion to the expected benefit” (Constitutional Council decision no. 2015-727, DC of January 21, 2016).

9. That is why some authors contest that it is an actual therapy in this case, because it is not about treating an existing individual but creating one who is healthy (Tina Rulli, The Mitochondrial Replacement ‘Therapy’ Myth, *Bioethics*, 2017, vol. 31/5, pp. 368-374). However, the context of mitochondrial donation remains a therapeutic one.

10 .A. Griffiths & al., An Introduction to Genetic Analysis, 2000, available at: https://www.ncbi.nlm.nih.gov/books/NBK21859/.

It is indeed because the mitochondria contain DNA that gene therapy and even germline gene therapy are mentioned, given that action is taken at embryonic level and that the modifications induced will be passed on to the next generations if the embryo concerned leads to the birth of a girl.[11] This viewpoint tends, however, to overlook the fact that no intervention on the nuclear genome takes place – it remains integral – and that the mitochondrial genes are not manipulated either.

As such, mitochondrial replacement therapy remains different from genome editing using a method such as CRISPR-Cas9, which is explicitly aimed at modifying the nuclear gene structure. The latter was the subject of an Inserm Ethics Committee position paper in February 2016, in which it was recommended to "respect the ban on all germline nuclear genome editing for human reproductive purposes and not to support requests to amend the legal conditions until the uncertainties surrounding the risks have been clearly evaluated, and until a broader consultation including the various civil society stakeholders has ruled on this scenario".[12]

11. National Academy of Science (NAS, *Mitochondrial Replacement Techniques*, Washington DC, The National Academy Press, 2016, p. 119 sqq. Il It must also be noted that the mitochondria supplied by the spermatozoa are destroyed within hours of fertilization by a mechanism that is being studied in mammals.
12. Available at: http://www.inserm.fr/qu-est-ce-que-l-inserm/l-ethique-a-l-inserm/saisines-et-notes-du-comite-d-ethique, (only available in French)

Research to benefit future children

In order to treat embryos correctly, therapies need to be based on research that will inevitably concern embryos – of other species and humans. Indeed, early embryonic development and the mechanisms that regulate it differ from one species to the next[13]. However, as the techniques increase in safety and efficacy, the number of embryos destroyed will decrease and the ultimate benefit to future children could prove considerable. The two approaches discussed in this document are already mature enough to have enabled the births of living and – so far to our knowledge – healthy children. In both cases, research on embryos has led to clinical applications, even if the preclinical research findings can still be considered insufficient.

Mitochondrial replacement therapy

The aim of mitochondrial replacement therapy is to prevent the transmission of maternal mitochondrial defects that are often responsible for severe diseases in children. These alterations are linked to mutations of the DNA constituting the mitochondrial genome. Mitochondria are organelles that produce the energy of our cells from glucose and oxygen metabolites. The mitochondrial components are coded in part by a genome specific to the mitochondrion (37 genes) and in part by the nuclear genome (some sixty genes). The exchange of mitochondria involves substituting maternal mitochondria with those of a female donor. Hence the “three-parent baby” expression used by some because two women contribute genetically to its creation in addition to the father. This expression is, however, misleading because it could equally be used in the event of oocyte donation in which two women contribute biologically to the creation of the child (genetic maternity *plus* gestational maternity). As we will see, maternity cannot be reduced to just its genetic component.

During fertilization, only the mitochondria of the ovum are transmitted to the embryo, meaning that mitochondrial diseases are transmitted maternally. To avoid this risk, it is envisaged to use a donor oocyte from which the nuclear genome is removed to replace it with that of the woman with the disease.

This can be done just before fertilization (*spindle transfer*), but the procedure is tricky because at this stage the chromosomes are organized around a mitotic spindle – a very fragile structure. In addition, the simultaneous transfer of a small amount of cytoplasm containing pathological mitochondria cannot be avoided. It is also possible to act just after fertilization, when the paternal and maternal pronuclei are properly visible and more easily transferable (*pronuclear transfer*) – therefore once the embryo is constituted. In the first case

13. Hélène Jammes, Patricia Faulque & Pierre Jouannet, Apport de l’expérimentation animale dans l’étude de la reproduction, de la procréation médicale assistée et du développement, *Bulletin de l’Académie nationale de médecine*, 2010, vol. 194/2, p. 301-317. See also Elo Madissoon & al., Differences in Gene Expression Between Mouse and Human for Dynamically Regulated Genes in Early Embryo, *Plos One*, 2014, vol. 9/8, p. 1-10.

it is an oocyte that is enucleated, whereas in the second, it is an early embryo[14] which, emphasizes John Zhang, can pose an ethical problem according to certain religious conceptions. That is why his team used the first technique, *spindle transfer*, to help a woman with Leigh syndrome have a healthy child. A male blastocyte was transferred of which 5.7% of the mitochondria remained carriers of the undesirable mitochondrial DNA mutation. In Leigh syndrome, an affected mitochondria rate of below 10% is generally linked to an absence of clinical symptoms. Postnatal testing found between 2 and 9% of the same mutation in various tissues of the child (urine, foreskin).[15] It being a boy, the mitochondrial mutations will not be passed on to the next generations. In August 2017, the US FDA demanded that John Zhang cease his clinical research, insofar as it involved the intentional creation of a genetically modified embryo.[16] The British authorities, however, after a lengthy and intense debate, authorized the clinical use of the second technique, without an embryo transfer happening to date.

In addition, a technique with similar consequences can be used to "revitalize" oocytes deemed to have little or no function.[17] In this case, donor oocyte cytoplasm is injected into the oocyte of the future mother with the spermatozoid that will fertilize it. As such, the child has the mitochondria of two different women. Allan Templeton stated in 2002 that this procedure had led to the births of some thirty children. Nevertheless, it was recommended not to pursue this technique due to a risk of chromosomal abnormality and epigenetic modifications.[18]

Treatment of triploidy

Some couples are unable to conceive normal embryos that can be transferred to the uterus, notably because they contain more than two pronuclei (generally three but can be as many as seven). Removing the extra haploid pronucleus (or pronuclei) at zygote stage (first embryonic cell) – and as such restore diploidy – is nevertheless an option. This was already successfully performed on a triploid embryo in 2002 and led to the birth of a healthy boy. This is a proof of principle that triploid embryos can be transferred to the uterus, implant and result in normal babies when their diploidy is restored.[19] Two situations can occur which cause triploidy. In the first and most common, two spermatozoa penetrate the ovum – in which case

14. Shoukhrat Mitalipov et Don Wolf, Clinical and Ethical Implications of Mitochondrial Gene Transfer, *Trends in Endocrinology and Metabolism*, 2014, vol. 25/1, p. 5-7.
15. John Zhang & al., Live Birth Derived from Oocyte Spindle to Prevent Mitochondrial Disease, *Reprod Biomed Online*, 2017, vol. 34, p. 361-368.
16 Letter dated August 4, 2017, available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM570225.pdf
17. Julie Steffann & al., Prévenir la transmission des mutations de l'ADN mitochondrial: mythe ou réalité ?, *Médecine/Sciences*, 2010, vol. 26, p. 897-899.
18. Allan Templeton, Ooplasmic Transfer – Proceed with Care, *New England Journal of Medicine*, 2002, vol. 346/10, p. 773-775. The first birth was that of a girl in 1997 (Jacques Cohen & al., Birth of Infant After Transfer of Anucleate Donor Oocyte Cytoplasm Into Recipient Eggs, *The Lancet*, 1997, vol. 350, p. 186-187).
19. Suresh Kattera et Christopher Chen, Normal Birth After Microsurgical Enucleation of Tripronuclear Human Zygotes: Case Report, *Human Reproduction*, 2003, vol. 18/6, p. 1319-1322.

two paternal pronuclei are observed. In the second, the polar body is not expelled – in which case there are two maternal pronuclei. Removing the additional pronucleus makes it possible to restore diploidy (i.e. the "normality" of the embryo) and therefore to recreate a (seemingly) normal embryo. The main difficulty resides in not getting the pronucleus wrong[20].

Ethical questions

Each time medical research performed on human embryos is concerned, ethical questions must be asked. In relation to the two approaches discussed here, these questions are of two types. Questions about the risks related to the techniques themselves (*safety* – not to be confused with *security*, which is often linked to questions of malicious use, such as when we refer to biosecurity) and questions of principle. The latter can be specific, when they concern just one or the other of these techniques, or general.

The question of safety

The question of safety is an ethical question insofar as it is immoral to put a patient at excessive risk.[21] "Excessive risk" means a risk that is not compensated by an expected benefit (beneficence) and that is not accepted by the person concerned (autonomy). For the same reason, the use of an ineffective method would be ethically unacceptable.[22] In terms of the two approaches discussed here, the requirement level must be identical to that needed for the use of any new treatment developed within the framework of medical research. This implies that the techniques have been clearly and fully described, that they have been validated by the requisite pre-clinical studies, that their clinical use had been approved by the appropriate and independent ethical and regulatory bodies, and finally that the means necessary to evaluate their consequences – particularly for the health of the children – are implemented.

However, particularly with regard to mitochondrial replacement therapy, its many safety concerns must be emphasized. The editorial of the *RMB Online* issue which features the article by Zhang and his colleagues notes the ongoing absence of evidence that nuclear transfer is without danger.[23] More precisely, Eunju Kang and her colleagues observed – in embryos having received mitochondrial replacement therapy by spindle transfer – a gradual reduction in healthy mitochondria in some cells and a return to the maternal haplotype, even though over 99% of the mitochondria had been detected from the donor just after the

20. Jacques Cohen & al., Rescue of Human Embryos by Micromanipulation, *Baillière's Clinical Obstetrics and Gynecology*, 1994, vol. 8/1, p. 95-116.
21. Whether or not this patient is a person.
22. In that sense, the question of efficacy is also a question of ethics. But these are two different questions: a technique can be safe but ineffective, or effective but high-risk.
23. Mina Alikani & al., First Birth Following Spindle Transfer for Mitochondrial Replacement Therapy: Hope and Trepidation, *Reprod Biomed Online*, 2017, vol. 34, p. 334.

transfer.[24] Another study, conducted in mice, also suggests caution because it showed that individuals with the same nuclear genes but different mitochondrial DNA did not have the same life expectancy and presented with diverse pathologies.[25] This is reminiscent of what happened to Dolly and suggests that mitochondrial replacement therapy could be responsible for serious health problems in the child at a later stage.

It must still be noted that the concern elicited by the existence of risks is particularly high when the changes induced are irreversible, which is the case when the intervention concerns the embryo and remains true even if there are therapeutic means of mitigating the undesirable effects of these irreversible changes.

These phenomena make it difficult to evaluate the risks related to this technique – risks which are linked to the mutable nature of living entities. Therefore, the good health of the children born up until now using these techniques is no guarantee for the future, to the extent that studies on the human embryo, while necessary, would not be an absolute guarantee of safety over the long term This situation is nothing new: the changing nature of risk is a particularity of all procreation procedures. The risks relating to these procedures are all the more difficult to ascertain in that during its early development, the embryo appears capable of self-regulating in order to eliminate at least some of the abnormalities in its cells. This phenomenon is still poorly known and understood, but while self-regulation appears possible when it concerns DNA or chromosomes, it is not likely to occur in triploidy[26].

As a consequence, ART is not without risk. This became evident once the ART techniques began to emerge, notably when IVF was developed and used in the clinical setting. Robert Edwards and Patrick Steptoe received intense criticism on the subject when Louise Brown was born, and later when intracytoplasmic sperm injection (ICSI) was used. While luckily nothing serious has occurred in the millions of children born as a result of IVF or ICSI, it cannot be transposed without further studies in the case of the approaches discussed here.

The questions of principle

Questions of principle are concerns that cannot be determined by a favorable calculation of the risks and/or by the consent of the person concerned (their consent). As such, some authors argue that even if the requirement for oocyte donation by women using ART could be fully justified in order to enable research or help other couples, it must continue to be forbidden because it constitutes an instrumentalization of women. Even if women

24. Eunju Kant & al., Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations, *Nature*, 2016, vol. 540, p. 270-275.
25. Ana Latorre-Pellicer & al., Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing, *Nature*, 2016, vol. 535, p. 561-568.
26. For these questions refer to Sabrina Ladstätter & Kikuë Tachibana-Kinwalski, A Surveillance Mechanism Ensures Repair of DNA Lesion During Zygotic Reprogramming, *Cell*, 2016, vol. 167, p. 1-14, ainsi que Masood Bazrgar & al., Self-Correction of Chromosomal Abnormalities in Human Preimplantation Embryos and Embryonic Stem Cells, *Stem Cells and Development*, 2013, vol. 22/17, p. 2449-2456.

consent, donation should be prevented in the respect of human dignity (instrumentalization being a paradigmatic violation of the latter).[27]

These questions of principle can be general or specific. They are general if they concern all ART practices and specific if they concern some or just one. As such, the ban on commercializing elements of the human body affects all practices – according to French law, it is illegal to sell one's gametes or embryos, or to rent one's uterus. However, the condemnation of eugenics can only affect, within the scope of bioethics, the practices that involve modification of the germline nuclear genome or the selection of gametes and embryos based on their genetic characteristics, whether they are pathological or not.[28] As can easily be seen, mitochondrial replacement therapy and the treatment of triploidy are not concerned by these criticisms. There is no question of commercialization because mitochondrial replacement therapy is a donation. And there is no question of eugenics, given that neither therapy affects the germline nuclear genome or destroys any embryos due to their properties. It is a matter of therapy each time. But are there any other ethical conundrums surrounding them?

Insofar as these are ART techniques and as such receive social and legal support, it is not necessary to reexamine in this document the objections in principle against ART.[29] Therefore, it is not necessary to give an opinion on the assertion that these practices violate human dignity, that they run contrary to solidarity or that they go against the natural order, because we could not direct them against ART in general. The only question that remains, apart from safety, is that of harm or injury. Do mitochondrial replacement therapy and treatment of triploidy, in themselves or as a result of their direct consequences, cause harm to any of the stakeholders?

It is easy to see that it is not the case: to treat forms the very vocation of medicine, and therefore of doctors. The parents request the therapeutic procedure and the future child (assuming that we can cause harm to an entity not yet in existence)[30] will benefit from it after their birth and, at least we can hope, throughout their life. As for the embryos, it has already been said, they are not people and what is more, far from suffering harm, they benefit here from a treatment that enables them, in the case of restoration of diploidy, quite simply to exist. That said, the currently applicable ethical rules and directives must, of course, be respected. If not, the stakeholders could suffer harm. Consider the case in which the consent of the parents is not sought or that it is obtained by manipulation or coercion, even if it is not

27. Bernard Baertschi, Human Dignity as a Component of a Long-Lasting and Widespread Conceptual Construct, *Bioethical Inquiry*, 2014, vol. 11, p. 201-211.
28. When sex selection is performed by PGD, the embryos are not carriers of pathological characteristics. The eugenics in question here is private or liberal eugenics, i.e. a choice made by the parents and not by the State – as was the case with political eugenics (Laurence Perbal, Eugénisme, in Gilbert Hottois, Jean-Noël Missa & Laurence Perbal, dir., *Encyclopédie du trans/posthumanisme*, Paris, Vrin, 2015, p. 287).
29. Of course, they can be the subject of discussion and controversy on the moral philosophy level. Same for research on embryos: there is a current legal and ethical consensus on its lawfulness, but this does not exhaust the philosophical debate on its subject.
30. Axel Gosseries, *Penser la justice entre les générations*, Paris, Aubier, 2004, chap. 1.

a plausible scenario here.

Mitochondrial replacement therapy could, however, raise doubts regarding parenthood, because the child is genetically derived from three different people ("three parents", according to the media[31]). A concern not shared by everyone and that is based on a very biological and even exclusively genetic conception of parenthood – as opposed to a social conception that does not ignore the role of the parental project, or that of gestation and emphasizes a parent-child relationship that is forged before birth and during childhood. Is this new form of parenthood likely to harm to the child? Only time will tell. Nevertheless, various forms of parenthood currently in existence (adoption, donor-assisted reproduction, blended families, single-parent families, etc.) have shown no such signs. The risk condemned in some quarters has not materialized and we cannot legitimately think that it will be the same here.[32] The fact that mitochondria are transmitted by the mother still signifies that the effect of the transfer will also be manifested in the offspring, unless all resulting children are boys – indeed only girls pass on their mitochondria to the next generations. Would it be problematic, even discriminatory, to enable only the transfer of treated male embryos in order to produce only boys? It is a question that we can ask, although it must be noted that it is not the opinion of the US FDA, for which a 2016 report recommends selecting only male embryos for the procedure.[33]

A more metaphysical concern sometimes put forward is that of a threat to individual identity.[34] Only mitochondrial replacement therapy is concerned here, given that the restoration of diploidy does not modify the individual's genome, often considered the basis of this identity. The response to this objection was that only the mitochondrial DNA is concerned, i.e. 0.1% of the human DNA. The mitochondrial DNA also does not appear to play a role in the phenotypic characteristics determining the structure (or essence) of the person. In its rejection of an appeal by the Jérôme Lejeune Foundation against a French research project concerning the interaction of the nuclear and mitochondrial genomes during embryo development prior to implantation, the Montreuil Administrative Court also emphasized the fact that there is no modification of the nuclear genome: "Neither the aim nor the effect of the approved project is to transfer foreign genes into the nuclear DNA of the embryos used".[35] As a consequence, some authors even assert that mitochondrial

31. Refer, for example to *Le Monde*, September 28, 2016: "Première naissance d'un bébé 'à trois parents'".
32. Regarding this issue, we would do well to consider this observation by Robin Marantz Henig: "The predictions of Watson in the 70s, like those who tried to prevent IVF from starting, have been proved wrong. We have not seen the breakdown of the nuclear family or the creation of soulless babies that people like Leon Kass were heralding […]. Today, Leon Kass uses the same language to express his fears in regard to cloning. Cloning threatens the dignity of human procreation, giving one generation unprecedented genetic control over the next, he wrote this year [2003] in an article in *The New York Times*. It is the first step toward a eugenic world in which children become objects of manipulation and products of will" (Pandora's Baby, *Scientific American*, juin 2003).
33. A. Bredenoord & J. Appleby, Mitochondrial Replacement Technologies: Remaining Ethical Challenges, *Cell Stem Cell*, 2017, vol. 21, p. 301.
34. Nuffield Council in Bioethics, *Novel Techniques for the Prevention of Mitochondrial DNS Disorders*, London, 2012, p. xv.
35. Montreuil Administrative Court, June 21, 2017 reading, p. 7.

replacement therapy should be compared to changing batteries, an expression which others see as an inappropriate trivialization of this technique.[36]

More profoundly, and most importantly, considering that what makes our identity or essence is identical to the human genome (nuclear and/or mitochondrial) or – a slightly less strong theory but with the same consequences – that our identity or our essence depends on it completely is based on an erroneous conception called “genomic metaphysics” by Alex Mauron[37] – other authors refer to “genetic essentialism”.[38] To counter such a conception, we will cite Richard Dawkins, who elegantly states: “There is no one-to-one mapping between bits of genome and bits of phenotype, any more than there is mapping between crumbs of cake and words of recipe”.[39] We can add that the majority of the genes have nothing to do with the essential properties that constitute our identity and reiterate that our genome underdetermines our behavioral and psychological traits. The natural and social environment (including at cellular level) plays a decisive role in what we are, including in the activation of some “dormant” genes.

In short, on the ethical level, the primary requirement for these two embryo therapy techniques is safety – in other words, the evaluation of risks and benefits. Certainly, mitochondrial replacement therapy occurs at genome level, which is not the case with the restoration of diploidy, but the sole purpose of this procedure is corrective and to restore good health. As such, we can place the two procedures on the same footing: it is about re-establishing health with a therapeutic objective for the embryo. It is in the name of this evaluation of the risks and benefits that, concerning mitochondrial replacement therapy – the only technique that has been the subject of debate, particularly in the English-speaking countries –, several people have spoken up to say that the transition to the clinical setting was premature. The UK, however, authorized it after a long scientific and democratic debate. In France, the discussion has not yet really taken place, but it is urgent that it begin. However, if we want a safe technique for parents and to avoid its practice by unscrupulous doctors in some countries – covertly or not –, further research is needed in these two domains, particularly in countries where ethical vigilance is high, such as France.

36. Garry Hamilton, The Mitochondria Mystery, *Nature*, 2015, vol. 525, p. 446.
37. Alex Mauron, Is the Genome the Secular Equivalent of the Soul?, *Science*, 2001, vol. 291, p. 831.
38. Camilla Kong & al., Psychiatric Genomics and Mental Health Treatment: Setting the Ethical Agenda, *The American Journal of Bioethics*, 2017, vol. 17/4, p. 4-5.
39. Richard Dawkins, Universal Darwinism, in David Hull et Michael Ruse, *The Philosophy of Biology*, Oxford, Oxford University Press, 1998, p. 22-23.