Evaluation of PReimplantation embryo Aptitude for DEvelopment (EPRADE)

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In spring 2020, a group of researchers – investigators of a French program for clinical research in hospitals (PHRC) entitled *Comprehensive Chromosomal Testing of Trophectoderm (Te) Biopsies of Blastocysts (Ctteb) to Improve Live Birth Rates After in Vitro Fertilization: A Prospective Randomized Trial*, sought the opinion of the Inserm Ethics Committee (CEI) regarding their project. This was on the informal advice of the French Agency of Biomedicine (ABM), despite the Ministry of Health's Directorate General for Healthcare Provision (DGOS) having already accepted and funded the program and before the French National Agency for the Safety of Medicines and Health Products (ANSM) had approved its performance.

Although issuing opinions on specific research projects is not one of the Committee's missions, it accepted the request taking into account the highly innovative and sensitive aspects of such research. Then, the Committee's Embryo and Developmental Research group wished to pursue its reflection, broadening it to encompass the general aspects of the evaluation of embryos resulting from IVF before transfer to the uterus for gestation and the ethical questions raised by this approach.

Hence, what this Memo will be looking at is the *Evaluation of PReimplantation embryo Aptitude for DEvelopment* (EPRADE). EPRADE must be distinguished from preimplantation genetic diagnosis (PGD), which is authorized in France "on an exceptional basis" when "the couple, due to its familial situation, is highly likely to give birth to a child with a particularly severe genetic disease accepted as being incurable at the time of diagnosis." Hence, the aim of PGD is to identify a genetic marker (gene or chromosomal) in at least one of the two parents which is liable to lead to a serious incapacitating disease in the child or be life-threatening. Legally authorized since 1994, PGD has a very strict regulatory framework, which is principally defined in articles L. 2131-4 et seq. of the *French public health code (CSP)*.

EPRADE must also be distinguished from any intervention aimed at identifying

specific characteristics in embryos, in order to select certain aspects of the future child. As such, this Memo does not address questions relating to the identification of sex chromosomes on the embryo, carried out with the aim of choosing the child's sex for reasons of personal or familial preference, a common practice in several countries.

This Memo is the fifth published by the CEI on the subject of embryo research. The first (2014) took stock of research on human embryos in France and its regulatory framework, formulating a certain number of proposals – notably the necessity to "improve the treatments and processes used to assist human reproduction." The second (2015) was centered around questions relating to the studies or research that could be undertaken on the embryo prior to its potential transfer for gestation. The third (2017) looked at questions surrounding research aimed at treating the embryo or performing interventions on it, for example, the donation of mitochondria to avoid the mother-to-child transmission of mitochondrial disease. Finally, the fourth (2019) reported on the deliberations made regarding research on embryos and embryonic models for scientific use (EMSUs).[1]

1. The context

1.1. The medical and scientific context

Fifty years ago, very little was known about the human embryo prior to implantation, insofar as it could only develop *in vivo* in the woman's uterus following natural conception. From 1978, and especially in the 1980s when IVF was possible and developed in many laboratories, the human embryo, neither person nor object, became a study "subject". It very quickly became apparent that the chances of pregnancy were markedly improved if IVF was not performed during a mono-ovulatory cycle but following hormonal stimulation to obtain multiple oocytes, leading to the formation of multiple embryos after fertilization. Therefore IVF did not lead to the formation of just one embryo but to a cohort of them. A heterogeneous cohort comprised of embryos whose morphological characteristics varied from the very first days of development. It was then realized that these characteristics had a bearing on the chances of achieving pregnancy and as such on the embryos' aptitude for development when transferred

1. These Memos can be consulted on the INSERM website: https://www.inserm.fr/recherche-inserm/ethique/comite-ethique-inserm-cei/saisines-et-notes-comite-ethique.

to the uterus. As a consequence, biologists classified embryos by the number and appearance of their component cells at a given time, by the quantity of cell fragments present next to the cells, and by the state of the nuclei within the cells.

Based on this classification, the embryo(s) considered to have the best aptitude for development were given priority for transfer to the uterus and/or frozen for possible future transfer, with the development of the other embryos interrupted. This strategy was deployed in laboratories worldwide and was never considered ethically inappropriate. However, it was challenged by decisions banning the freezing of surplus embryos for reasons of avoiding the creation of stocks which could be destroyed if not needed for gestation. This was the case in Italy where a law was voted in 2004 allowing IVF with no more than three oocytes, banning the freezing of embryos, and imposing their transfer to the uterus irrespective of their state. In the country's IVF centers in 2006, three embryos were transferred in over 50% of treatment cycles, leading to spectacular results. A 12.6% delivery rate, falling largely below the 20% average achieved by the other European countries that year (explained by the lack of choice of the embryos transferred) and a 23.8% delivery rate of multiple babies, which was higher than that of the other European countries (explained by the high proportion of triple-embryo transfers).[2] In 2009, the Italian Constitutional Council declared the 2004 law to be unconstitutional, the law was changed, and Italy's results fell in line with those of the other countries.[3]

IVF centers have always sought to achieve the highest possible pregnancy and delivery rates in order to reduce the number of attempts needed for couples to be successful and to reduce the constraints, risks, and emotional difficulties that can arise with each treatment cycle. Reducing treatment repetition is also of interest when it comes to reducing financial costs. Added to this objective is that of ensuring that pregnancies and their outcomes take place under the best conditions to ensure the safety of mother and child.

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2. J. De Mouzon & al., "Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE", *Human Reproduction*, 2010, vol.25, p. 1851-1862. See also P. Jouannet & al., Peut-on réduire le risque de grossesse multiple après fécondation in vitro? , *Bulletin épidémiologique hebdomadaire*, 2011, vol. 23/24, p. 261-262.

3. In Switzerland, the law banned the creation of more embryos than could immediately be implanted, in order to avoid freezing them. This was overturned in 2011 following a referendum.

Very significant progress has been made in this area over the past forty years, essentially based on improvements in laboratory techniques:

- The development of appropriate culture media has made it possible to develop embryos up to the blastocyst stage (day 5), making it possible to avoid the transfer of embryos whose development would have stopped earlier, as is the case for example when the activation of the embryonic genome, which usually starts at the eight-cell stage (day 3) does not take place.
- Improvements in embryo freezing techniques, particularly vitrification, have made it possible to obtain embryos whose aptitude for development after thawing is similar to that of unfrozen embryos. Through the use of this technique, it is sometimes envisaged to vitrify the entire embryo cohort at the blastocyst stage (freeze all) for future transfers, when the hormone stimulation used prior to oocyte harvesting is considered to have harmful effects on the uterine mucosa, with the risk of disrupting implantation.
- Video microscopy has made it possible to observe with greater precision the kinetics of the embryos' first cell cycles and their morphological evolution by minimizing disruptions to their culture conditions.

In France, IVF centers are required to communicate all of their results to the ABM, which publishes an annual national summary.[4] In 2018, a total of 58,210 oocyte harvests were performed for intraconjugal IVF – i.e. with the gametes of the future parents. These harvests led to the collection of 572,987 oocytes, an average of around 10 per puncture. Fertilization led to the formation of 300,479 embryos, averaging around five per attempt. Among them, 56,222 embryos were transferred in the days that followed (18.7%), 81,115 were frozen (27%), and 163,148 (54.3%) were deemed unsuitable for transfer and freezing. It must be noted that in over 15% of attempts, the embryos were not transferred immediately but were all frozen for a subsequent transfer (*freeze all*). The 56,222 embryos transferred in the days following IVF resulted in 9,770 women delivering 10,510 children (18.7% of the embryos transferred). The same year, out of the 53,019 thawed embryos, 47,523 were transferred, resulting in 8,054 women delivering 8,409 children (15.9% of the thawed embryos and 17.7% of the transferred embryos).

4. https://rams.agence-biomedecine.fr/activite-intraconjugale.

These results show a very marked improvement trend when compared with those published by the ABM over the past 15 years. They nevertheless show that the embryos created by IVF have very little chance of becoming a child, because in over 90% of cases they do not have the capacity to develop correctly. Is this situation the consequence of IVF? It is not possible to claim this because we know that during natural conceptions in humans, the majority of embryos self-destruct more or less early on in their *in vivo* development,[5] which explains to a certain extent our species' low level of fecundity.

Nowadays, the chances of a couple having a child are higher than 20% per IVF attempt (regardless of the number of embryos transferred) and the number of women giving birth is practically the same, whether or not the embryos had been frozen first. In addition, the delivery rate of multiple babies has significantly decreased (10.4% in 2018 versus around 19% in 2008), the latter result being mainly due to a change in the embryo transfer strategy. Indeed, in 2018 in France, 56.2% of transfers were performed with one embryo versus 42.3% in 2015 and 26.5% in 2008. There is a strong international consensus recommending single embryo transfer because this offers the best chances of having a child, whilst avoiding where possible multiple births, which can lead to complications. This objective may be achieved not just by improving the procedures but also by being able to identify, within the cohort, the embryo with the best chances of developing. While much progress has been made in this area, it is still not enough, because among the embryos considered to have the best aptitude for transfer and development, less than 20% lead to the birth of a child. That is why many researchers are trying to identify the biomarkers that would best characterize the embryos with the best aptitude for development prior to their transfer to the uterus.

1.2. The regulatory context

Regarding basic or preclinical research on embryos that cannot be transferred to the uterus for gestation, the protocols must be authorized by the ABM in accordance with article L2151-5 of the CSP.

Clinical research projects as part of medically assisted reproduction on embryos

5. See G. Benagiano G & al., "Fate of fertilized human oocytes", *Reprod Biomed Online*, 2010, vol. 21, p. 732-241, and A. J. Wilcox & al., Preimplantation loss of fertilized human ova: estimating the unobservable, *Human Reproduction*, 2020, vol. 35, p. 743-750.

likely to be transferred to the uterus must be authorized by the ANSM. The provisions applicable to this research differ from CSP article L2131-4 concerning PGD.[6]

- During natural conceptions in humans, the majority of embryos self-destruct more or less rapidly during their *in vivo* development.
- Following IVF, fewer than one in two embryos deemed able to develop are transferred to the uterus and/or frozen for future transfer.
- Less than 20% of transferred embryos currently lead to the birth of a child. Hence the necessity to be able to identify the biomarkers that would best characterize the embryos with the best aptitude for development prior to their transfer to the uterus.

2. Evaluation of PReimplantation embryo Aptitude for DEvelopment (EPRADE)

If we are to improve the success rate of IVF, it is necessary to conduct studies on the embryo in order to find the best biomarkers of its aptitude for development. This is not just a technical question of efficacy but also an ethical requirement, given the significant distress caused by implantation failures and miscarriages to couples undergoingAssisted Reproductive Technologies (ARTs). Indeed, reducing unnecessary suffering is morally important and one of the aims of medicine.

One way is to improve the *in vitro* culture media in which the embryos are placed, which we know can improve implantation and pregnancy rates, as well as the development of children following IVF.[7] We can also try to improve our knowledge of the embryos' intrinsic characteristics by analyzing their biomarkers. The wide variety of methods that may be used for this analysis include simple observation, microscopic evaluation of the embryos' morphological characteristics (as has been done since the beginning of IVF), or video-microscopic analysis of their cell cycle kinetics. It is also possible to indirectly evaluate metabolic functions by measuring the chemical composition of the culture medium in which the embryos are placed; these are referred to as non-invasive methods.[8]

6. This was discussed in our Memo "État de la recherche sur l'embryon humain et propositions" (Part 2), June 2015.
7. C. Bouillon & al., "Does Embryo Culture Medium Influence the Health and Development of Children Born after In Vitro Fertilization?" , *PLoS ONE*, vol 11, 2016, e0150857.
8. D. K. Gardner & al., "Diagnosis of human preimplantation embryo viability", *Human Reproduction Update*, 2015, vol. 21, p. 727-747.

The methods become more invasive when the analysis concerns embryonic cells sampled on day 3 of development (eight-cell stage) or extra-embryonic cells (trophectoderm) at the blastocyst stage. But the same type of invasive method is routinely practiced when PGD is performed and this type of sampling is not known to create any major disruptions in the subsequent development of the embryo and so does not decrease (or decrease by much) the chances of pregnancy.[9]

The knowledge acquired in this domain varies widely and the research is at different stages. Sometimes this research is of a basic or preclinical nature aimed at establishing links between given biomarkers and embryonic development. If links are established, clinical research is performed to establish the indications, efficacy, and safety of the methods.

2.1. The new EPRADE methods studied at the clinical research stage

2.1.1. Evaluation of chromosome status

In recent years, the majority of studies have focused on the marker of balanced chromosome content (euploidy).[10] We know that most embryos that are not euploid spontaneously interrupt their development before birth. Yet at the blastocyst stage (day 5-6 of development), around 30% of the embryos are not euploid when the woman is under 35 years of age – a proportion that gradually rises to 70% at the age of 41.[11] These differences explain to a large extent the decrease in IVF success rates according to the woman's age irrespective of the technique, as shown by the overview drawn up by ABM for 2018 (Table 1).

9. J. C. Harper & al., "The ESHRE PGD Consortium: 10 years of data collection", *Human Reproduction Update*, 2012, vol. 18, p. 234-247.
10. K. Sermon & al., "The why, the how and the when of PGS 2.0: current practices and expert opinions of fertility specialists, molecular biologists, and embryologists", *Molecular Human Reproduction*, 2016, vol. 22, p. 845-857.
11. J. M. Franasiak & al., "The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening", *Fertility and Steril*ity, 2014, vol. 101, p. 656-663.

Maternal age	IVF	ICSI	FET
< 30 years	26.7%	27.4%	22.9%
30-34 years	24.3%	24.9%	22.6%
35-37 years	19.4%	18.6%	19.3%
38-39 years	14.6%	16.4%	14.6%
40-42 years	7.9%	7.4%	9.6%
> 42 years	1.7%	5.0%	1.7%

Table 1: *Delivery rates according to maternal age and technique used:* IVF = standard in vitro fertilization, ICSI = intracytoplasmic sperm injection, FET = frozen embryo transfer.[12]

Analysis of the embryos' chromosomal content at the blastocyst stage enables us to know whether there are modifications to the number of chromosomes (aneuploidy) in their cells. This may concern a missing chromosome (monosomy) or an additional chromosome (trisomy) in one of the autosome pairs or at sex chromosome level. Such analysis also shows the chromosome concerned by the trisomy or monosomy if the embryo is aneuploid, and estimates the degree of mosaicism, i.e. the proportion of embryonic cells that carry the chromosomal modification. In practice, such analysis is performed on several cells taken from the trophectoderm (extra-embryonic tissue).

Knowing that the embryos' chromosomal status can vary within the same cohort, how should their transfer be approached? This question has been broadly discussed within the relevant medical and scientific communities, leading to recommendations drawn up by the *Preimplantation Genetic Diagnosis International Society* (PGDIS).[13] Embryos can be divided into three categories following chromosomal analysis:

1. Euploid embryos or mosaic embryos with no more than 20% abnormal cells, which are given priority for transfer.

12. https://rams.agence-biomedecine.fr/activite-intraconjugale.

13. D. S. Cram & al., "PGDIS Position Statement on the Transfer of Mosaic Embryos", *Reproductive Biomedicine Online*, 2019, vol. 39 Suppl 1, e1-e4.

2. Embryos carrying a homogenous aneuploidy that we know cannot lead to the birth of a child, which are never transferred.
3. Embryos carrying a homogenous aneuploidy that is compatible with the birth of a living child and mosaic embryos. In this case, the choice of the embryos to transfer should be made according to the risk of stopping development, according to their type of aneuploidy and degree of mosaicism.[14]

However, despite the many studies carried out, it still has not been demonstrated for certain that embryo chromosomal content is a criterion to use systematically to improve IVF results in all cases. And two questions are raised here: is the chromosomal status of the trophectoderm cells identical to that of the embryonic cells? Does the embryo possess regulatory mechanisms to eliminate the aneuploid cells? Such a phenomenon could play a decisive role, especially when the embryos are mosaic[15].

In France, a PHRC, accepted and funded by the French Directorate General for Healthcare Provision (DGOS) is expected to start soon. It aims to evaluate the utility of a chromosomal analysis of embryos to determine their transfer to the uterus when IVF is performed in women aged 35 to 41.

2.1.2. Evaluation of metabolic status

The metabolic activity of the embryo is determined from the very start of its preimplantation development both by its intrinsic characteristics and by external factors relating to the culture conditions that influence its viability. Different methods of analysis have been proposed in order to determine the choice of the embryos to be transferred, especially near-infrared spectroscopy, whose utility has been evaluated in four randomized clinical trials including around 1,000 women. A Cochrane review of these four trials concludes that IVF results are not improved by this approach.[16]

14. F. R. Grati & al., "An evidence-based scoring system for prioritizing mosaic aneuploid embryos following preimplantation genetic screening", *Reproductive Biomedicine Online*, 2018, vol. 36, p. 442-449.
15. M. Yang & al., "Depletion of aneuploid cells in human embryos and gastruloids", *Nature Cell Biology*, 2021, vol. 23, p. 314-321.
16 C. S. Siristatidis & al., « Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies (Review) », *Cochrane Database of Systematic Reviews*, 2018, vol. 3, art. CD011872.

2.2. From methods to current research and prospects

In 2008, during a retrospective analysis of blastocyst trophectoderm cells, a team of Australian and Greek researchers found that the transcriptome (the type of RNA present in the embryo reflecting gene expression) differed in the embryos depending on whether or not they had led to the birth of a child.[17] The researchers therefore suggested including this analysis in the strategy adopted in order to identify the most competent embryos for transfer. However, it is difficult to have a sufficiently precise and reliable technique for RNA profile analysis at single-embryo level. In a recent pilot study, an ultrasensitive technique made it possible to identify 47 transcripts expressed in a significantly different way in the trophectoderm cells of blastocysts having led to pregnancy.[18] This finding must however be confirmed before envisaging the clinical use of this type of marker.

If embryos that are apparently identical in morphological terms can differ in their transcriptomic profiles, it is logical to think that the proteins produced by early human embryos may also vary – and this has been confirmed by an experimental study.[19] This observation led to the analysis of the proteins secreted in the culture medium during the embryos' *in vitro* development. Using mass spectrometry, a research team identified, in the culture medium on day 3 of development, 14 peptides whose profile made it possible to distinguish the embryos with the best or least good chances of implanting.[20] It was using the same type of approach that a French team showed that the level of the soluble form of CD146, a membrane glycoprotein acting among other things as regulator of trophoblast migration, was significantly weaker when retrospectively assayed in the culture medium of the embryos that had implanted.[21] The utility of this biomarker which is not correlated to embryo morphology must be confirmed by a prospective study.

From the simplest to the most sophisticated, many technologies have been and will continue to be developed in order to characterize those biomarkers capable of

17. G. M. Jones & al., "Novel strategy with potential to identify developmentally competent IVF blastocysts, *Human Reproduction*, 2008, vol. 23, p. 1748-1759.
18. P. Ntostis & al., Can trophectoderm RNA analysis predict human blastocyst competency? , *Systems Biology in Reproductive Medicine*, 2019, vol. 65, p. 312-325.
19. M. G. Katz-Jaffe & al., Proteomic analysis of individual human embryos to identify novel biomarkers of development and viability", *Fertility and Sterility*, 2006, vol. 85, p. 101-107.
20. J. Nyalwidhe & al., "The search for biomarkers of human embryo developmental potential in IVF : a comprehensive proteomic approach", *Molecular Human Reproduction*, 2013, vol. 19, p. 250-263.
21. S. Bouvier & al., "Soluble CD146, an innovative and non-invasive biomarker of embryo selection for in vitro fertilization", *PLOS One*, 2017, vol. 12, e0173724.

identifying the human embryos conceived by IVF which have the best chances of implanting and leading to the birth of a child. While much progress has been made, current findings suggest that it is illusory to think that one single biomarker will be enough to fully meet the objective. It is likely that the best results will be obtained by combining analyses, a difficult challenge when it comes to obtaining information on embryos with small numbers of cells and residing in just several microliters of culture medium. Many research studies, basic, preclinical, or clinical, remain to be carried out on the human embryo to improve the results of IVF

3. An overview of the ethical questions raised by IVF

On July 28, 1978, in Oldham, UK, Louise Brown was born as a result of IVF – a medically-assisted reproduction (MAR) technique or assisted reproductive technology (ART). Although she was the first test tube baby (an expression used back then), others soon followed in her wake, including Amandine in France, born on February 24, 1982. In *L'Œuf transparent*[22], Jacques Testart recounts the story of her birth and the development of the techniques that made it possible. In the industrialized countries, the number of babies currently born through MAR accounts for 1.5 - 3.5% of all births depending on the country, which is far from being negligible.

This story marked the beginning of the medicalization of reproduction,[23] which brings new moral responsibilities into play, as is the case each time human beings direct a natural process for their benefit.

MAR has traditionally been aimed at fulfilling infertile couples' desire for a child, a desire that Aristotle likened to a "natural impulse which acts both upon plants and animals also, for the purpose of their leaving behind them others like themselves".[24] As is the case with any animal, the reproductive instinct is very strong in the human species. But unlike "natural" procreation (through sexual intercourse), MAR uses artificial means and above all separates the different aspects of the reproductive act, as Testart highlights, evoking a reverse image of contraception: "No

22. Paris, Flammarion, 1986.
23. Strictly speaking, the medicalization of reproduction began even earlier than that, with the first artificial inseminations performed at the end of the 19th century.
24. *A Treatise on Government*, I, 2.

sooner has contraception separated 'normal' sexuality from procreation than IVF can exclude it."[25] This separation of the sex act from conception has for a long time constituted the main objection of the Catholic church against unnatural procreation techniques: "Never is it permitted to separate these different aspects to the point of excluding positively either the intention of procreation or the conjugal relation," affirmed Pius XII.[26]

The idea that nature must serve as our guide has often been prevalent, particularly when it comes to sexuality. Regarding the artificial nature of contraception, Gabriel Hardy made this remark at the start of the 20th century: "We reproach these means as being against nature. And they certainly are. An indifferent Goddess, neither kind nor cruel, nature offers the best and worst of things. Discerning and enjoying the best, avoiding and preventing the worst, modifying for our greatest good the impassive course of natural phenomena, that is progress."[27] What counts for Hardy, are not the ends and limits that nature imposes on us, but those that we choose freely and in our interest, as well as that of our children.

Nature is not always beneficent towards human beings, and this can be seen with procreation: with natural procreation, the majority of embryos conceived do not lead to a child being born. As mentioned previously, even with *in vivo* fertilization in the uterus, over 50% of the embryos are considered to self-destruct. Following IVF and transfer to the uterus, an even higher proportion of embryos do not develop. This must be taken into account in the uterine transfer strategy, which is what justifies EPRADE. It is therefore a form of anticipating or preventing a risk that in any case already exists. Here, like elsewhere, medicine attempts to compensate the weaknesses of nature (considered from the viewpoint of human interests).[28]

This debate on the natural purposes and the question of the respect that is or is not owed to them, although heated, is now in the past, with IVF forming one of the socially accepted methods of MAR, even if some practices remain strongly contested,

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25. *L'Œuf transparent*, p. 24.
26. « Stérilité conjugale et insémination artificielle », 1956, in P. Verspieren, dir, *Biologie, Médecine et Éthique*, Paris, Le Centurion, 1987, p. 42. Currently, this objection has taken a back seat in favor of the arguments centered around the moral status of the embryo.
27. *L'avortement*, Paris, éd. du Malthusien, s. d., p. 177.
28. It must be noted that MAR can still involve other types of dissociations, consecutive for example to embryo freezing (temporal) or to the donations of gametes and embryos (filiation).

such as the donation of gametes.[29] As far as IVF is concerned, the ethical viewpoint is currently more specifically focused on the question of embryo use in research which, it must still be emphasized, is necessary to improve pregnancy rates.

When conducting research on embryos, the first question raised is that of their *moral status.* The CEI discussed this in its Memo entitled *Research on Embryos and Embryonic Models for Scientific Use (EMSUs)*,[30] concluding in the wake of other bodies, such as the *National Consultative Ethics Committee for health and life sciences (CCNE)*, that the human embryo conceived by IVF is not a person, but a potential person, which in principle does not prohibit tests on it that may lead to its destruction. We will not revisit the subject here. However, what we will examine are the objections to the use of technologies and criteria for evaluating and prioritizing the transfer of those embryos most capable of implanting and leading to the birth of a child. The objections most often raised are the following:

a) this choice would involve sorting and it is immoral to sort embryos,

b) this choice would constitute the instrumentalization of embryos,

c) this choice would manifest a eugenicist attitude,

d) this choice would mark the start of a slippery or fatal slope,

e) this choice would devalue some people with disabilities.

a) This choice involves sorting and it is immoral to sort embryos

In our 2017 Memo, entitled *From Embryo Research to Therapy*, we wrote that there is sorting of embryos "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). Sorting 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".[31] It must however be acknowledged that the term "sorting" often has negative connotations in debates, just like "selection", especially when it implies that its aim is to promote the existence of some individuals that we wish to be born rather than others. Other terms, such as "choice"

29. The debate on the respective value of what is natural and what is artificial, whilst still ongoing, has shifted its focus to biotechnologies, especially GMOs.

30. January 2019, p. 12-13, available at: https://www.hal.inserm.fr/inserm-02111023/document.

31. December 2017, p. 4, available at: https://www.inserm.fr/sites/default/files/media/entity_documents/Inserm_Note_ComiteEthique_GroupeEmbryon_decembre2017.pdf.

or "diagnosis" do not have this connotation, like expressions of more general meaning underlining the cognitive rather than the volitional aspect of the process, like "evaluation" or "estimation". The acronym EPRADE refers to evaluation, emphasizing that the choice of the embryo in question must be based on objective data.

It is important to adopt an appropriate expression because the word represents the thing, but what is central to reflection in biomedical ethics (and elsewhere) is not the word, but the thing. As such, referring to "choice" as we are doing and continue to do raises no semantic issues if we describe precisely what it covers. What is it about? The purpose of the process is to increase the percentage of transfers that lead to births; therefore it is about prioritizing transfer to the uterus of the embryo with the greatest chances of implanting and leading to a birth. In order to determine what that embryo is, it needs to be evaluated and qualified as having "aptitude" for implantation and development (and nothing else), and it requires the definition of markers to characterize that aptitude. Once the evaluation has been performed, the embryo with the best score in relation to those markers (and only those markers) is chosen. As such, the choice is made based on an *evaluation*: it is the capacity for implantation and development that presides over the entire process, because it would be morally unacceptable to transfer an embryo with almost no chances of implanting if there are others whose chances of development are better. But ultimately, this choice remains a human decision, and in this decision, as we shall see, the parents must take center place.

Such a procedure involves *screening* or *sorting*, because some embryos will be prioritized, but this is an inevitable and minimally morally problematic consequence of many choices: choosing *a* from three objects *a*, *b* and *c* according to the criterion Z implies that we sort *a*, *b* and *c* according to their degree of conformity with Z, and that if we choose *a*, it is as a function of and only as a function of Z. Therefore, unlike what the objection affirms, such sorting is in itself no way immoral, because it is an operation induced by any choice as soon as it involves a certain number of objects. Certainly, we may prefer another term, as has been said, but this changes nothing. In addition, choosing on the basis of an evaluation implies that we subject *a*, *b*, and *c* to an *analysis* or *test*, then do a *diagnosis* on *a*, *b*, and *c* according to the meaning of this term in the Larousse dictionary as designating "all of the measures, checks that are performed in order to determine or verify the technical characteristics of a system."[32] However, as we have already said, it is not about

32. https://www.larousse.fr/dictionnaires/francais/diagnostic/25154.

PGD as it is defined by French legislation, because it is not a question of identifying a potential genetic abnormality of the embryo, existing in one and/or the other of the two parents, which is intrinsic to it and which will determine what it will later become, but a relational characteristic (its capacity to implant and develop *in* a uterus)[33] which is generally not indicative of what it will become. In short, were EPRADE to be the subject of a specific regulatory framework, it would have to differ from that currently envisaged in France for PGD.[34]

b) This choice constitutes the instrumentalization of embryos

Among the ethical taboos that are very commonly evoked, there is that of unjust instrumentalization, which is considered to be a violation of dignity. The argument goes back to Emmanuel Kant who, in the second formulation of the categorical imperative, affirms: "Act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as means only."[35] Therefore, were choosing an embryo to involve instrumentalizing it, EPRADE would be morally unacceptable because, although an embryo is not a person, it still belongs to humanity – not just because it is biologically human but also in that it is sociologically the fruit of a parental project.[36]

Instrumentalizing, i.e. reducing somebody to the state of a simple means, may be taken in two ways: one subjective, the other objective. In the objective sense, it is an action that violates a person's autonomy or dignity, whether or not they are conscious, whether or not they are suffering in their flesh. In the subjective sense, the person must be aware of this and suffer as a result. Can we say that in EPRADE the embryo is instrumentalized objectively and despite the intention of the researchers and doctors, whose aim is to best fulfil the parents' desire for a child? Their request may also be considered as instrumentalizing because, even if their desire for a child is legitimate, they resort to illegitimate means when requesting or accepting the

33. Here, "intrinsic" and "relational" are taken in their logical sense: a property is intrinsic when it implies no link with anything else (e.g. the embryo *is human*), it is relational if a link is implied (e.g. the embryo *develops* in the uterus).
34. It would therefore be desirable that the legislation adopt provisions to provide the necessary clarification.
35. *Groundwork of the Metaphysics of Morals,* sect. 2. For the link between instrumentalization and dignity, cf. B. Baertschi, art. "Dignité" *L'Encyclopédie Philosophique*, available at: http://encyclo-philo.fr/dignite-gp/.
36. P. Jouannet, B. Baertschi & J.-F. Guérin, *Recherches sur l'embryon : dérive ou nécessité ?*, Paris, Le Muscadier, 2019, p. 45-68.

evaluation of their embryos.[37]

Upon reflection however, it appears that evoking the concept of instrumentalization to characterize EPRADE is irrelevant, because this concept is about wanting to impose one's own aims on a third party and here no aim is imposed on the embryo to be transferred – it is simply granted a chance to develop and be born. Certainly, the embryo is a means for the parents to satisfy their desire to have a child, but this is the case with any intention to procreate. This point merits further development because it is often a source of misunderstanding.

It is often said that a child must be wanted for itself. But while it is a common expression, it lacks meaning because the child does not exist yet, and it is refuted every day by many of our educational practices: a child is generally wanted in order to cement the love of its parents and then, when it is born, it is molded according to the desires of those parents (among other people). As for certain non-egotistical motivations of the past pushing people to procreate, such as the encouragement of natality for the purposes of war, their moral value may be doubted – in the France of the beginning of the 20th century, Hardy lamented: "It is the obsession of the repopulators to continuously set our inferiority against Teutonic superiority."[38]

Would wanting a child therefore be an immoral enterprise? This appears absurd and yet is the child not conceived as a means, and therefore instrumentalized? Susan Gibson[39] considers that such a deadlock comes from the fact that our view is too focused on a specific episode, namely conception and the reasons presiding over it. Indeed, procreation is just one point in a lasting process that brings parents and children together; therefore, while it remains true that the act of conception is done by and for the parents, it would only be morally reprehensible if the entire parental relationship were to remain polarized in this way. Having a child from the viewpoint of one's personal fulfilment as a parent is no doubt inevitable, but from that, the child conceived is, in Kantian terms, an end in itself and must be considered as such. That is why someone who wants a child in order to have a being to love and who, little by little, forms a deep relationship with it, cannot be reproached. For Gibson, what is important is

37. It must be noted that the criticism relating to instrumentalization can go in several directions. Refusing to choose between embryos and asking that they all be reimplanted could be seen as instrumentalizing the woman's body.

38. *L'avortement*, p. 293.

39. "Reasons for Having Children: Ends, Means, and 'Family Values' ", *Journal of Applied Philosophy*, 1995/3.

how the child will be treated later, once it is born; if it is treated or envisaged to be treated according to the personal dignity it is supposed to have, then the reason for its conception is morally correct. As such, in the case of the EPRADE that concerns us, choosing a specific embryo to transfer to the uterus following IVF constitutes just one moment in the realization of the desire for a child, and referring to instrumentalization in this respect is inappropriate.

What counts here from the moral point of view are not the parents' motivations, but how the child is and will be treated; choosing an embryo according to its chances of development and birth does not amount to reifying it or treating it like an object.

c) This choice manifests a eugenicist attitude

As we have seen, some embryonic markers are morphological, while others are molecular or genetic. These markers are not all equivalent, whether in terms of their reliability or the representations they convey. The genetic markers raise different questions, given their accompanying representations and possible consequences of their use. Therefore, it could be feared that choosing a genetic marker implies a eugenicist attitude, because it involves selecting a trait that is characteristic of the embryo's heritage.

To this objection, there is first a short and direct response: it is not relevant, because looking for markers of successful implantation and development is not equivalent to selecting traits of the unborn child or person. The sole objective of transferring a euploid embryo is to reduce the risk of miscarriage rather than seek to encourage (or avoid) the birth of a child that fulfils certain genetic characteristics. Therefore, such preimplantation selection simply amounts to avoiding the transfer of an embryo whose development would spontaneously stop during pregnancy. As we have already said in this Memo, it is the embryo with the highest score in relation to the identified markers that is chosen, and nothing else. The same could not be said if, subsequent to EPRADE, the choice of embryo to transfer were to fulfil other purposes. Indeed, analyzing the chromosomal status of the embryo makes it possible to detect aneuploidy and also to know the sex of the embryo. Future parents could therefore request the preferential transfer of embryo(s) which would lead to the birth of a boy or a girl. This possibility, accepted in some countries, raises ethical questions that differ from those

raised by EPRADE[40], and are not discussed here.

A less direct response nevertheless seems necessary, given the prevalence of objection for reasons relating to eugenics.

Going on the hypothesis (albeit already refuted) that EPRADE involves choosing an inherent characteristic of the embryo, would this be morally problematic? To answer this question, we must reiterate what we said earlier in this Memo: it is necessary to examine precisely what the words cover, and this is especially important when they are emotionally loaded, as is the case when eugenics is evoked. As soon as we tackle it, we immediately see that the eugenics in question here has nothing to do with the traditional eugenics of Francis Galton's time, or with the eugenics prevalent in the industrialized countries at the start of the 20th century, because back then it was about improving the species (or at least halting its degeneration: it was about acting at the collective rather than individual level), by using the coercive power of the State without recognizing the parents' procreative freedom. In addition, it was about "*sorting*" the genitors (separating the good – who were encouraged, from the poor – who were discouraged) and not the embryos. On all these points, current eugenics, referred to as liberal because it is based on the parents' procreative liberty, opposes traditional or political eugenics. Certainly, they can both have the same effects and consequences because the preimplantation tests (PGD) lead to the non-implantation of many embryos with abnormalities or serious malformations, but the nature of the intention behind it and purpose associated with it differ considerably and, with the exception of not wanting to take it into account, like the strict utilitarians, it must be emphasized that the differences in intention and purpose make a moral difference.[41]

This point is important because once differences have been brought to light when we study a practice (descriptive and conceptual step), it remains to be determined whether they mark a moral difference, given that many descriptive and conceptual differences have no ethical impact. Here, in addition to the question of intention and purpose, such an impact is manifestly observed, given that the presence or not of autonomy has fundamentally moral meaning, and that the

40. W. Dondorp & al., ESHRE Task Force on ethics and Law 20: sex selection for non-medical reasons, *Human Reproduction*, vol 28, 2013, p. 1448-1454.

41. Another difference is that traditional eugenics applies to what is or what we suppose is transmissible to the child; yet aneuploidies are only infrequently transmissible: for example, in the few women with trisomy 21 who have had children, the trisomy is transmitted in only 30% of cases. This constitutes an additional reason for differentiating EPRADE from PGD.

practice concerns adults or embryos, entities whose moral status differs.

It must be noted that for law there is eugenics when a society promotes a practice (whether medical or not) that is systematically aimed at deleting genetic characteristics in the next generation because it considers them to be negative. Therefore, France's civil code could not say that it is forbidden to implant all embryos which carry the variant characteristic of Huntington disease: this would make it guilty of eugenics.

d) This choice marks the start of a slippery or fatal slope

"The refusal of eugenics is a widely shared principle, but where does eugenics begin? Is wanting a child who is as healthy as possible part of it" [42] asks the CCNE. We may consider the question to be at least partially rhetorical, and that the answer must be no. But if we accept this first step, namely that the tests are justified because they fulfil the desire of having a healthy child, do we not risk being led to accept others, such as widespread liberal, resolute eugenics or even a coercive policy in the end? Therein lies the argument of the slippery or fatal slope. What is it worth?

Jean-Yves Goffi specifies that there are two versions of it: a *logical* version, in which we slide down the slope because there is no good reason to stop at any specific point, and a *psychological* version which states that once we have yielded on a first point, we are required to do so for the next points.[43] In his work *Moral luck*, Bernard Williams introduces another useful distinction: the slippery slope argument takes two forms, that of the *horrible result*, focused on what is at the bottom of the slope and that of the *arbitrary result*, which denounces the slide, because it renders arbitrary all the distinctions we could make.[44]

Those who fear the start of a fatal slope often use the four forms of the argument; those who oppose it do so in the name of two considerations: either they deny that the slide is possible or probable, or they emphasize that it is the particularity of norms to introduce limits: for example, the laws on abortion state until what point in the pregnancy it is permitted, thereby creating a normative frontier. This limit is of course arbitrary in a sense (it varies by country and epoque), but what is not arbitrary is setting limits.[45] This last consideration appears to us to be

42. *Rapport de synthèse du Comité Consultatif National d'Éthique*, Les Ulis, EDP Sciences, 2018, p. 43.
43. *Penser l'euthanasie*, Paris, PUF, 2004, p. 32-33.
44. "*Which Slopes are Slippery", in M. Lockwood, ed., Moral Dilemmas in Modern Medicine*, Oxford, OUP, 1986, p. 126.
45. B. Williams, *op. cit.*, p. 134.

decisive: laws and regulations institute limits; certainly, it sometimes happens that they are not respected and that they are overturned; however this has nothing to do with a slippery slope, but simply with illegality. It may also be that the limits are shifted and replaced by others, in accordance with societal evolutions or normative considerations: it is the legislator's privilege to do this; but again, this is not a fatal slope phenomenon, but a desired and controlled normative change. If EPRADE has a legal framework, it will thereby escape any slide.

e) This choice devalues certain people with disabilities

The markers that indicate a low chance of the embryo transfer leading to the birth of a child include the trisomies and as such trisomy 21. Yet the detection of this chromosome abnormality using PGD and prenatal diagnosis (PND)[46] has been condemned by some authors and associations because it would express a discriminatory attitude towards both the disability and the carrier of the trisomy, which could ultimately lead to decreases in the quality of care of such patients and their social stigmatization, as well as that of their parents who, in "allowing" them to be born have placed a burden on society. The literature refers to the *expressivist argument*: the practice of tests in general would *express* a stigmatizing attitude not just towards the disability but also towards those with that disability, whose lives would be perceived as being of less value.[47] Is there a real risk?

It is doubtlessly not the case because the risk has not materialized regarding the treatment of people with disabilities: their care has improved greatly over the past century. They are also better accepted, as emphasizes the CCNE: "In recent years, the quality of life of those affected has been improved by better management."[48] Regarding EPRADE, it must be reiterated that the expressivist argument is of no relevance because – again – trisomies are not screened for in so much as they make it possible to partially predict the fate of the person to be born, but that they are markers of absence of success of transfer to the uterus, a relational and not inherent characteristic of the embryo.

The question of how those with disabilities are received and supported in our society

46. French legislation prohibits the detection of trisomy 21 in PGD but allows it in PND. PND is also done with this in mind in most cases.

47. S. Wilkinson, *Choosing Tomorrow's Children*, Oxford, OUP, 2010, chap. 6 and Nuffield Council on Bioethics, *Genome Editing and Human Reproduction*, July 2018, p. 82.

48. CCNE, *Opinion on ethical issues in connection with antenatal diagnosis*, Opinion no. 107, 2009.

largely goes beyond the context of IVF in which the choice of an embryo to transfer expresses the desire of the parents to not have a disabled child and has no political dimension in itself.

- The objections most often put forward against the techniques involving a choice between embryos are:
  (a) that this choice would involve sorting and that it is immoral to sort embryos,
  (b) that this choice would constitute the instrumentalization of the embryos,
  (c) that this choice would manifest a eugenicist attitude,
  (d) that this choice would mark the start of a slippery slope, and
  (e) that this choice would devalue certain people with disabilities.
- While these objections raise important ethical questions, they do not concern a technique such as EPRADE, notably because it does not evaluate the intrinsic characteristics of the embryos but only their aptitude for implantation and development.

4. From objections to benefits

As is often the case when ethical questions are raised, we focus on the concerns and objections: first do no harm, medical ethics tell us. Of course, but it is even better to be beneficent. Now that we have shown that the ethical concerns most often raised do not affect EPRADE, or at least do not call it into question at a fundamental level, we must reiterate that it is a source of benefits for the couple.

First and foremost, the aim of EPRADE is to improve the chances of pregnancy and, as such, satisfy the couple's desire to have a child. Given that this desire is generally accepted as legitimate, what favors its satisfaction constitutes a benefit, in principle. And it is precisely this to which contributes EPRADE, by reducing the number of treatments needed to fulfil the couples' desire to become parents and therefore the distress that necessarily accompanies the failures. We have already said that reducing unnecessary suffering is morally important and constitutes one of the aims of medicine.

For this parental project to be fulfilled under the best conditions when IVF is involved, the decision needs to be taken in agreement with the couple: it is the couple that initiates the request and it is the couple that can step in regarding

whether or not an embryo is transferred and, if there is more than one embryo, which embryo must be transferred. Indeed, we have already said that not all embryos have the same potential for implantation and development. It is certainly morally desirable for priority to be given to the most suitable embryos, but this does not prevent, following evaluation of the embryos' potential, a choice having to be made to determine (1) those to transfer immediately (as a priority), (2) those to freeze for future transfer, and (3) those that will not be stored. The question of knowing the criteria used for this classification also merits being asked before the IVF is performed but it does not overshadow what is decisive from the ethical point of view: that information is available to the future parents enabling them to give their opinion in an informed manner and, if necessary, make the final decision when choosing the embryo to be transferred.

The religious representatives – Catholic, Muslim, and Jewish – who were interviewed during the preparation of this Memo all insisted on the central role of the couple and of the woman in the decision-making process. There can be said to be a broad consensus on this point.

5. Towards recommendations for good practice

If the concepts of evaluating embryonic development prior to implantation and choosing embryos for transfer to the uterus based on the results of EPRADE are deemed ethically acceptable, what should be done in order for these activities to be conducted responsibly and under conditions that respect the ethical principles and convictions of everyone?

In answer to this, two types of scenarios must be distinguished: that of research and that of the implementation of these approaches within the framework of IVF programs.

5.1. Research

The medical purpose of this research and the undeniable progress that its expected results could promote represent sufficiently substantial arguments in favor of not only authorizing but also encouraging basic, preclinical, and clinical research in the field. In France, such research can be conducted within the framework of the currently applicable legislative and regulatory texts.

However, two key points deserve emphasis:

- Depending on whether they exclude the transfer for gestation of embryos having been the subject of research (basic and preclinical research) or whether they allow it (clinical research), the research projects must be approved by different organizations (ABM and ANSM) according to different procedures. This provision is complex and represents a major obstacle to the relevant and efficient framework of projects. Given the specific nature of the questions relating to research on embryos, one sole organization with all the necessary scientific and ethical competences, should be tasked with authorizing all human embryo research projects, whatever they are. To date, ABM is the organization which appears to be the best placed to fulfil this mission. This recommendation has already been formulated in a previous Memo.[49]
- Currently, systematic pleas are filed with the administrative justice seeking to cancel research authorizations that have already issued. Analysis of the arguments developed by those making the objections and the judgements issued allow us to conclude that these pleas are (scientifically and ethically) inappropriate in most cases, as well as abusive. They nevertheless create an extremely unfavorable context for conducting quality research in this domain in France.[50]

5.2. The deployment of EPRADE in IVF programs

Currently and based on morphological evaluation, we do not transfer embryos that have no chance of leading to the birth of a child (> 50% of embryos). These embryos are neither transferred nor frozen and their development is stopped. Among the other embryos, priority is given to transferring those with the best capacities for development *in utero*. This is the strategy that all IVF centers have used over the past 40 years and it raises no particular concerns.

The use of a new EPRADE technique in routine practice should only be envisaged if it has demonstrated its efficacy and safety as is envisaged for any technique according to the provisions of article L 2141-1 of the CSP. The purpose of EPRADE and its consequences for the resulting strategy, in terms of the choice of embryos transferred to the uterus, must be clearly explained beforehand to those receiving IVF, so that they can consent to this new procedure or opt for the

49. See État de la recherche sur l'embryon humain et propositions, Part 2, June 2015.
5050. Given that these actions are based on points of law, it could be hoped that legal specialists find a way to bring an end to their abusive repetition.

traditional evaluation of morphological criteria[51].

When the marker being evaluated by EPRADE is genetic, whether it relates to the chromosomes or genes, the strategy must specify what will be proposed should the marker be able to identify potentially viable children. For example, when the aim is to detect aneuploidy, EPRADE can identify embryos with trisomies or monosomies that are likely to lead to miscarriage but are not incompatible with the birth of a living child. That is why genetic counselling should be offered prior to IVF if this type of EPRADE is envisaged. Then, and when EPRADE and the choice of embryo to transfer to the uterus are implemented, those receiving IVF must be able to participate in the decisions made, with their opinions even being decisive if such decisions concern whether or not to transfer an embryo likely to potentially lead to a child that is viable, but probably or certainly disabled or functionally impaired. For example, if EPRADE observes that the embryo is a carrier of trisomy 21, the decision may be made not to transfer it. Indeed, it cannot be considered unacceptable to terminate a 5-day-old embryo *in vitro* when French legislation allows the termination of a several-week-old embryo or fetus *in utero*. However, if the future parents, who have been clearly informed of the consequences of their choice, decide that the embryo with trisomy 21 should be transferred, then that transfer must be performed and the future parents informed of the means available to accommodate and manage the needs of the resulting child under the best possible conditions.

51. The information and consent relating to EPRADE are included in the provisions envisaged in articles L 2141-2 et seq. of the CSP.

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Nelly Achour-Frydman, reproductive biologist (Clamart-Antoine Béclère)

Odile Lacroix, reproductive biologist (Marseille-La Conception)

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Virginie Rio, cofounder of the BAMP collective

Patricia Fauque, reproductive biologist (Dijon)

Mgr Pierre d'Ornellas, archbishop of Rennes

Rivon Krigier, rabbi at the Adath Shalom synagogue (Paris)

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List of abbreviations

ABM: French Agency of Biomedicine

MAR Medically-assisted reproduction

ANSM: French National Agency for Medicines and Health Products Safety

CCNE: National Consultative Ethics Committee

CEI: Inserm Ethics Committee

CSP: French public health code

DGOS: French Directorate General for Healthcare Provision

PGD: Preimplantation genetic diagnosis

EPRADE: Evaluation of PReimplantation embryo Aptitude for DEvelopment

IVF: *In vitro* fertilization

EDR: Embryo and Developmental Research (EDR) group of the CEI

ICSI: Intracytoplasmic sperm injection

EMSUs: Embryo models for scientific use

PGDIS: Preimplantation Genetic Diagnosis International Society

ART Assisted reproductive technology

PHRC: Program for clinical research in hospitals

FET: Frozen embryo transfer

Glossary

Autosome: Chromosome that is not a sex chromosome.

Blastocyst: Embryo, 5 to 7 days after fertilization, made up of around 200 cells. It is at this stage that the embryos are transferred to the uterus.

Aneuploid cell: Cell with an abnormal number of chromosomes, for example monosomy (one chromosome instead of two) or trisomy (three chromosomes instead of two).

Euploid cell: Cell with the normal number of chromosomes (22 pairs of autosomes and two sex chromosomes).

In vitro culture: Specific culture conditions and media that reproduce the natural medium, enabling the development of an embryo in the laboratory following *in vitro* fertilization.

Preimplantation genetic diagnosis: Technique used to detect gene or chromosome abnormalities in embryos conceived through IVF, before they are transferred to the uterus.

Prospective study: Study evaluating the effects of exposure to a given factor, technique, or any other form of intervention.

Eugenics: The various methods and practices whose objective or effect is to promote in the next generation individuals who carry selected traits based on their genetic heritage.

In vitro fertilization: Fertilization of an ovum by a spermatozoon in the laboratory, in a culture medium.

Metabolic functions: Functions enabling the functioning and development of cells or an organism. For example, breathing, digestion, blood circulation, ...

Genetic marker: Identifiable genetic sequence found at a specific location of the genome.

Mitochondrion: Small organelle enabling a cell to function correctly. A type of small "energy center".

Embryonic model for scientific use: embryonic models used by researchers. For example, to better understand embryonic development, understand the effect of genetic modifications, ...

Embryonic mosaicism: Coexistence of two (or more) cell types that differ for one or more genes (or chromosomes) in an organism. For example, when a genetic mutation occurs in a cell at a very early stage of embryonic development, the cells of this line will all carry the mutation that will be absent in the other cells of the organism.

Mass spectrometry: Technique used to detect and quantify molecules.

Trophectoderm: Layer of cells at the periphery of the blastocyst that will give rise to extra-embryonic tissues such as the placenta.

Vitrification: Ultra-rapid freezing technique that preserves the integrity of the cells.