

Opinion n°107

Opinion on ethical issues in connection with antenatal diagnosis:
Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)

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Introduction

In recent times, technical developments in genetics, medical imagery and assisted reproduction have transformed prenatal medicine. Such changes responded to society's legitimate expectations for healthcare and prevention. For example, thanks to advances in prenatal medicine, the number of induced therapeutic abortions following a prenatal diagnosis of rubella or toxoplasmosis has dropped sharply from several hundred a year not very long ago, to just a few today.

But at the same time there is an uneasy feeling among members of the medical professions and the general public alike: what should rightly be done when a foetus' condition is too severe for medical management? Is there not a risk that prenatal medicine could, unwittingly, lead to discrimination as to who will be born? Can we reconcile our egalitarian and humanist society with selective prenatal practices?

On the one hand, the dignity of human beings is not conditioned by their intellectual capacities or physical abilities. On the other, the sufferings that a human life will be enduring may lead to transgressive decisions, out of humanity.

This tension between the intention of protecting an initially welcome human life and taking suffering into consideration is central to prenatal medicine, characterised by increasingly sophisticated tools for monitoring pregnancies — or the selection of embryos conceived *in vitro* — leading to some births being prevented. In this Opinion¹ the Committee will seek to clarify the ethical issues arising out of this situation and will also extend its consideration to include a prospective analysis beyond the more immediate reference to the implementation of, or the amendments to, the currently applicable bioethics legislation.

The expression "antenatal diagnosis" will be designating the two types of tests the law regulates:

- on the one hand, *prenatal* diagnosis (PND), consisting in discovering embryonic or foetal anomalies during pregnancy. It may play a major role in the medical management of the child, either during the gestational period itself or after delivery. It may also, in other cases, lead to parents requesting "induced abortion for medical reasons"²;
- on the other hand, *preimplantation* genetic diagnosis (PGD), following *in vitro* fertilisation to induce pregnancy, and consisting in a selection of embryos unaffected by the genetic disorder under research.

The use of these diagnostic techniques raises grave and complex ethical issues when a decision on whether a human being will be, or will not be, born needs to be taken. Some

¹ Note: This Opinion comes as a complement to three previous Opinions. The National Consultative Ethics Committee (CCNE) has already discussed issues raised by the extension of preimplantation diagnosis (N° 72), genetic information in the event of medical necessity (N° 76) and prenatal diagnosis of cystic fibrosis (N° 83). It also follows on from the issues discussed in Opinion N° 105 "Questions for the Estates General on Bioethics".

² Note: In this Opinion, the generic term is used. In the French Code of Public Health, mention is made of "Induced abortion for medical reasons" cf. Book II containing three chapters: Induced Abortion, chap. I: General Principles (art. L.2211-1 et 2); chap. II: Induced abortion before the end of the 12th gestational week (art. 2212-1 à 2212-11); chap III. Induced abortion for medical reasons (art. 2213-1 à 2214-5).

dilemmas are common to both techniques, others are more specific to one or the other. The fact, for instance, that PND may lead to late termination raises a more serious set of problems than is the case for PGD where the subject of debate is an *ex utero* embryo comprising a few cells. Inversely, PGD gives rise to ethical issues that do not apply with PND: embryo selection and the destruction of affected embryos.

To see our way clear out of this complexity, four lines of thought were followed in the Opinion:

- Before any ethical reflection, the issue of the *purpose* of antenatal diagnosis must be considered. How pertinent are the frequently used concepts of "prevention" and "eugenics" in this connection? (I).
- With the current law, the disorder must be both *severe* and *incurable* to qualify for induced abortion for medical reasons (following PND) and embryo selection (concurrently with PGD). However, severity is not something that can be categorised in general terms for a given disease: each case has to be judged on its own merits. The question then arises of the extent to which couples concerned can participate in the determination of the degree of severity of the foetal anomaly or the genetic disorder affecting their family (II).
- The similarities between the two diagnostic tools sometimes give the impression that PGD is an early form of PND. But in that case, how do the two fit together? Should embryo selection be considered solely as an alternative to induced abortion? Should extensions to screening for Down's Syndrome be a possibility when embryo selection is performed as part of a PGD? (III).
- Finally, electronic access to unproven genetic tests using embryonic DNA in a pregnant woman's blood, the results of which are made available while elective abortion is still legal³, raises new ethical issues created by the risk of hasty unassisted decisions to abort. These issues must be considered now, before the problem arises (IV).

³ The legal lapse of time allowed for elective induced abortion for emotional distress, is 12 weeks gestation time (or 14 weeks amenorrhoea).

I. Why diagnose?

I.1. The situation now

Without going into the technical details of PND and PGD, the following points are essential for an understanding of the ethical debate these techniques give rise to.

I.1.1. Prenatal diagnosis (PND)

a) Currently, to investigate morphological anomalies, PND is performed by foetal ultrasound and other medical imagery techniques or by chorionic villus or amniotic fluid sampling, or even using cord blood, for genetic or infectious diseases. A special chapter below (pages 23-24) concerns cell-based PND testing and the examination of foetal DNA circulating in the bloodstream of pregnant women (an early diagnosis technique now in the process of development).

b) Prenatal *diagnosis* should not be confused with prenatal *screening*. Using various tests, screening identifies an at-risk group in a population of pregnant women. Screening is a process of detection of suspected disease or disability based on systematic and non-invasive investigation. The two *screening* tests offered to pregnant women are ultrasound testing for foetal malformation and screening for Down's syndrome (trisomy 21) and certain kinds of aneuploidy⁴, which combines taking into consideration the mother's age, maternal serum markers, nuchal translucency⁵ and craniocaudal length⁶. Ultrasound screening also has the advantage of being able to detect multifoetal and ectopic pregnancies. Screening, therefore, can lead to further testing, in particular diagnostic ultrasound and/or PND requiring foetal sampling.

c) The need for PND is partly dependent on the quality of screening tests. Suspected foetal anomaly cases become rarer as and when the tools for screening them improve so that recent recommendations in favour of "combined screening"⁷ for trisomy 21 (now recommended for first-trimester screening) are opportune. Using these new practices should make it possible to have a more precise quantitative evaluation of risk, a corresponding drop in numbers in the "at-risk" group and, consequently, in the number of invasive procedures (puncture to obtain foetal biological samples).

d) While the offer for a biological PND is made, in most cases, at the time of screening for aneuploidy or following the discovery by ultrasound of a presenting

⁴ Aneuploidy: an abnormal number of chromosomes. Aneuploidy may refer to an extra chromosome or to a missing chromosome.

⁵ Nuchal translucency: a anechogenic zone viewed by ultrasound situated between the skin at the nape of the neck and the spine. It usually measures a few dozen millimetres but is greater in the case of Down's syndrome.

⁶ Craniocaudal (crown-rump) length correspond to the distance between the crown of the cephalic pole and the rump. This measurement estimates the age of pregnancy, plus or minus 3 days, between 7 to 13 weeks of amenorrhoea. This is the reference measurement for an assessment of gestational age. Nuchal lucency varies with gestational age.

⁷ Cf. a recent decree published in the *Journal Officiel* (dated June 23, 2009) setting out good practice rules for prenatal screening and diagnosis including maternal serum markers for trisomy 21 (www.legislationfrance.gouv.fr).

symptom, it can also be motivated by the existence of a known genetic disorder in the makeup (genic or chromosomal) of one parent, in that parent's family or affecting an older child. The existence of a family history is the trigger for PND in a tiny minority of cases⁸, but with the current legislation, it motivates all the PGD indications.

I.1.2. Ethical problems arising out of current PND practices

In ethical terms, two problems are very closely linked; one concerns PND iatrogenic risks (particularly in cases where invasive procedures are necessary), the other is in connection with the information provided to parents.

The first of these problems arises out of the miscarriages following foetus sampling. The foetus is lost in 0.5 - 1% of cases. It is true that the exact number of foetal lives lost as a result of amniocentesis or trophoblast biopsy performed because of echographic presenting symptoms cannot be calculated with any degree of accuracy. A certain number of pregnancies would probably not have come to term precisely because of the anomalies that were discovered. The loss of a foetus cannot therefore be attributed systematically to amniocentesis. It is, however, true that the loss of a significant number of foetuses free of the disease under investigation is a serious violation of the principle of proportionality which requires that means must be in keeping with the aim pursued.

The second problem is linked to the information given to parents involved in the prenatal screening and diagnosis procedures. As things stand at present, careful practices can, at most, hope to diminish, but not eliminate altogether, the risk of foetal loss. The quality of information supplied to parents is crucial⁹ in view of the possible consequences of amniocentesis or trophoblast biopsy and because the decision to undergo, or not, abortion for medical reasons, may be conditioned by this information. Three aspects determine the quality of information: a) plurality of options, b) neutrality, c) the time factor:

a) Plurality of options: PND legitimacy is reinforced proportionately to the diversity of purposes it serves: alleviating anxieties generated by an ultrasound screening procedure, offering medical treatment, neonatal surgery, transfusion, preparing for the birth of a sick or disabled child. Information has true ethical value if it clarifies the various options for possible action without dictating a choice.

b) Neutrality of the information¹⁰: when parents are informed of the possibility of abortion for medical reasons, it is particularly important to choose one's words with

⁸ Gene tests only represent 2.3% of these examinations. The breakdown for other biological tests is the following: 81% are cytogenetic (the main indication being suspected trisomy 21), biochemical for suspected non closure of the neural tube (11%), infection testing for toxoplasmosis or viral infection (5%). Furthermore, some examples of sampling are motivated by monitoring or treatment for foetal pathologies.

⁹ It is for this reason that the first decree dated June 23, 2009 setting out rules of good practice as regards prenatal screening and diagnosis for trisomy 21 cannot be read separately from the second decree of the same date concerning the information, the request for, and the giving of, consent by pregnant women to procedures bearing on maternal serum markers and giving rise to sampling and testing with a view to prenatal *in utero* diagnosis as provided for in article R.2131-1 of the Code of Public Health, www.legislationfrance.gouv.fr

the greatest care. Simply mentioning that pregnancy could be terminated may be interpreted as an encouragement to do so if the doctor, tacitly, considers that there is reason for concern. The information may be even more worrying because it is expressed in statistical terms. Information containing a statistical component and therefore combining what is known with what is unknown, cannot be anything but difficult to grasp for parents.

Irrespective of the motive parents may have for requesting a diagnostic procedure after screening, freedom of choice is a principle which cannot be questioned without encroaching on the fundamental rights of individuals.

c) The time factor: one of the preconditions for unconstrained reflection is time; parents' rights can only be guaranteed if they are given sufficient time to consider their decision. It also gives the doctor occasion to repeat information and assist a couple in taking a decision. Between screening and a possible PND, there is a waiting time which can be usefully given over to forward thinking. In practice, however, only rarely is the lapse of time between the two procedures put to this use. A large number of pregnant women do not fully apprehend the significance of antenatal screening¹¹. It is therefore essential that the time required to provide quality information on the consequences of screening be allowed for parents¹². Also, time for assisted reflection should be systematically set aside when parents are advised of foetal disability because such news may be so traumatic as to be incapacitating, and counselling required to help them take however long they need before arriving at a final decision

With the extension of combined screening and, even more so, with the implementation of PND based on foetal cells or DNA circulating in the maternal bloodstream, the indestructible link between time for reflection and freedom of decision is all the more worth emphasising.

¹⁰ Cf. Article 35 of the Code of Medical Deontology (article R.4127-35 of the Code of Public Health: "Physicians are duty-bound to provide honest information to those they examine, treat or advise (...)").

¹¹ Cf. Seror V. Ville Y., "Prenatal screening for Down syndrome: women's involvement in decision-making and their attitudes to screening" in *Prenatal Diagnosis* 2009; 29: 120-128., 05/01/09 www.interscience.wiley.com
This article highlights the gaps in the information given to women when they are offered trisomy 21 screening. The material is based on an enquiry within a population of nearly 400 women giving birth in a maternity home in Poissy from April to October 2005; over 88% of them had been screened. An analysis of the questionnaire they were given shows that 30% had not understood the results of the blood test and that the majority were unaware of the possible implications of the screening procedure or did not understand them. Furthermore, 50% had not considered the fact that screening could lead to amniocentesis and, as a follow-up, the offer of abortion for medical reasons.

¹² Cf. Article 33 of the Code of Medical Deontology (article R.4127-33 of the Code of Public Health): "Physicians must always take the greatest care and all the time required when establishing a diagnosis."

I.1.3. Biological diagnosis of embryos conceived by *in vitro* fertilisation (also known as "preimplantation genetic diagnosis")

Biological diagnosis¹³ of the cells of an embryo conceived by *in vitro* fertilisation (IVF), a technique often referred to as preimplantation genetic diagnosis (PGD), consists in identifying embryos which could be reimplanted in the uterus once they are seen to be free of the genic or chromosomal hereditary disease under investigation¹⁴.

PGD may also be helpful in rare circumstances, when a familial condition has been diagnosed only in grandparents. The parent concerned does not wish to know whether he or she is a carrier for the genetic mutation causing this disorder, but wants to avoid transmitting it to descendants. Is it acceptable to know for others what we do not wish to know for ourselves? It is true that insofar as respect for an individual's autonomy does not harm anyone else and, on the contrary in this situation, is inspired by the wish to avoid transmitting a serious and incurable genetic disease to an unborn child, it does not seem unethical to comply with such a request. Nevertheless, there are outcomes which cannot be ignored. The mother will have to undergo ovarian stimulation and oocyte retrieval. An evaluation of the benefits derived from the procedure known as "exclusion PGD" therefore supposes that sufficient time for specific information and counselling will be set aside.

The social judgment passed on PGD varies with individual value systems. Some people are inclined to underline the negative consequences, i.e. the elimination of the embryos carrying a genetic disease during the selection procedure. Others prefer to insist on the trauma caused by abortion for medical reasons which PGD can help to avoid. For couples who would otherwise have refrained from having a child because of the strong possibility that they would be transmitting a genetic disease, PGD makes it possible for them to consider parenthood. In this light, PGD is inspired by compassion that French law is justified in condoning.

This difference in outlook concerning PGD depends on the status granted to the embryo. Granting the embryo a dignity identical to that of an existing person leads purely and simply to dismissing PGD entirely since the end result is the destruction of affected embryos.

According to figures now available to us, some 300 applications¹⁵ to centres licensed for PGD are made by parents every year in France. In 2007, 50 children were born

¹³ The Code of Public Health, Chapter 4: preventive medicine concerning children; Section 3: "Biological diagnosis based on cells sampled from an embryo *in vitro*, Article R162-44".

¹⁴ *In vitro* fertilisation can provide several embryos outside the mother's uterus. When the embryos reach the 8 cell stage (three days after fertilisation), one or two cells are sampled in each embryo for genetic testing. If one, at least, of the embryos is free of the genetic defect, it will be reimplanted (on the 4th day) in the hope that a child unaffected by the genetic condition concerned will be born. Depending on whether the anomaly concerned is present or absent, the other embryos are either destroyed or kept for later implantation.

¹⁵ According to data supplied by the *Agence de la Biomédecine* (ABM) (biomedical agency), in 2007, 308 cycles were started, 244 oocyte retrievals were performed, 165 embryos were transferred, 55 pregnancies began, 41 women gave birth, 50 children were born.

following the procedure¹⁶. Although an ethical issue does not become less acute because it only concerns a small number of couples, these figures must not be totally ignored in a social context where ethical issues connected to PGD are frequently emphasised in comparison with the PND figures which concern tens of thousands of couples.

I.1.4. Inadequate resources for PGD

Today, there are three PGD centres in the whole of France. The fact that their resources are inadequate to cope with the number of couples whose application has been accepted is a problem. The waiting time for parents keeps lengthening despite a frequently dramatic family history. Depending on centres, the time elapsing before a request is made and the first PGD attempt varies between one and two years. As the woman's age increases, this waiting time may signify that chances of success are lost.

As a result, couples sometimes seek alternatives, not all of which are satisfactory: some resign themselves to going abroad to get PGD testing for which French resources are unavailable. Others choose *in vitro* fertilisation under the misapprehension that standard control procedures for the embryos before reimplantation will avoid some of the risks incurred by spontaneous conception. In some cases, couples decide to forgo PGD altogether and even abandon their plans to have a child.

In these circumstances, the Committee considers that PGD centres must be given the staff and the structures they need to be able to apply the law and satisfy couples whose requests meet the "serious and incurable genetic diseases" criteria. To achieve this, planning for more PGD licensed PGD centres¹⁷ is required.

For this to be done, France needs to have more licensed PGD centres and their creation should be set in motion.

I.2. Ambiguity of certain categories applied to antenatal diagnosis

I.2.1. Background concerning the role of the *Centre pluridisciplinaire de diagnostic prénatal* (CPDPN) (Multidisciplinary Centre for Prenatal Diagnosis) and the need for collegiality.

The end purpose of antenatal diagnosis raises ethical issues if the information is acquired once treatment is no longer possible, either during gestation or in the post-natal period, because the foetal condition that was detected is severe and incurable. In France, certification that this is the case signifies that if a pregnant woman so requests, termination for medical reasons will be allowed or PGD will be performed. Such certificates are delivered by a CPDPN. These multidisciplinary centres are expert hospital departments set up in not-for-profit healthcare institutions and licensed by

¹⁶ <http://www.agence-biomedecine.fr>

¹⁷ In the event that private centres were to be authorised so as to respond to the expectations of couples on the waiting list, the Committee considers that they should be controlled (via the 'good practices' guide) by public health authorities just like the currently licensed centres.

the *Agence de la Biomédecine* (ABM). They are staffed by obstetricians, geneticists, paediatricians, foetopathologists, ultrasound specialists, genetic counsellors and psychologists¹⁸ whose task is to provide advice and counsel on diagnosis, therapy and prognosis. The procedure, based on discussion, is well-suited to the need for collegial decision-making which is the safest way to limit diagnostic error risks and to check the validity of parents' requests for termination or embryo selection.

I.2.2. Can the purpose of antenatal diagnosis be described as "preventive"?

The Code of Public Health includes PND in the list of "preventive action relating to the child"¹⁹, on the same footing as articles relating to health records, mandatory medical examinations, nutrition and advertising. But integrating PND to prevention in this way does create problems. With health-related subjects, the word *prevention* is used to describe all the measures taken to reduce the risk of being ill or limiting the consequences of sickness²⁰. It is true that as far as antenatal diagnosis is concerned, several investigations are fully preventive in their purpose: treatment for toxoplasmosis, preventing rhesus incompatibility, hormone treatment for adrenal hyperplasia, organising the neonatal medical management of malformations and diseases for which treatment must be immediate. Through such objectives, PND does help to reduce neonatal mortality and prevent some disabilities. To that extent, there is undeniably a preventive element in favour of the unborn child (which currently gives rise to further care in 15% of cases²¹). However, the reference to "prevention" is more doubtful as regards one of the possible outcomes, i.e. induced abortion for medical reasons, and it is just as debatable when applied to embryo selection in the course of PGD.

It would be allowable to consider, of course, that medically motivated abortion or embryo selection "prevent" parents from suffering moral hardship, but to use the concept of "prevention" in this way is to risk losing sight of the fact that it is first and foremost in the direct interest of the subject involved that screening or diagnosis must be performed. The legitimacy of this use for the "prevention" concept can therefore be only partially applicable. By renouncing the use of the "prevention" category, French law would move further in the direction of the semantic and cultural evolution that began with abandoning the former category called "therapeutic" termination and the law

¹⁸ There are 48 of these in France, approved by the *Agence de la Biomédecine* (ABM) for a period of five years.

¹⁹ Cf. Code de santé publique (Sous la dir. de F. Dreifuss-Netter), Édition LexisNexis, 2009 : Deuxième partie : Santé de la famille, de la mère et de l'enfant, Livre I : Protection et promotion de la santé maternelle et infantile, Titre III : Actions de prévention concernant l'enfant, Chapitre Ier Diagnostic prénatal. (Articles L2131-1 à L2131-5). (Health of the family and of mother and child. Protection and promotion of maternal and infant health. Prevention in favour of the child. Prenatal diagnosis).

²⁰ Prevention appeared as a medical concept at the end of the 19th century with the development of the first vaccines. Together with lifestyle counselling and information campaigns, in the view of the public at large, vaccination is still today the main thrust of prevention, the aim being to prevent the onset of serious health problems. But there are in fact two other levels of prevention: "secondary" prevention, i.e. screening, with the aim of detecting a disease at the earliest symptoms (e.g. breast cancer) and "tertiary" prevention which seeks to prevent relapses or complications, so as to help patients live with their condition.

²¹ In 2005, 1149 therapeutic procedures directed at the foetus were performed out of a total 6441 certificates of severe disorders (cf. "*L'état des lieux du DPN en France - Agence de la Biomédecine*", Feb. 2008, p.p 27-28).

dated March 4, 2002 (which states that "being born cannot in itself be cause for claiming to have suffered a loss or moral wrong"²²).

Let us note, furthermore, that if it were considered that performing a therapeutic termination comes under the heading of prevention, then legal measures regarding information to be given to relatives should apply unambiguously. In fact, the Committee considers that "prevention" is not an appropriate wording to describe action to be taken by persons undergoing tests to inform their relatives of the risks incurred by an unborn child²³. In any event, according to CCNE, the expression "*prévenir une naissance*" (birth prevention) — to which the current Code of Public Health in fact lends credibility — seems excessively paradoxical.

The fact that termination for medical reasons (and the same could be said of embryo selection) does not aim *stricto sensu* to prevent ill health in the embryo does not lead to the conclusion that avoiding the birth of a child is a purpose completely alien to ethical considerations. Medical reasons for terminating a pregnancy are multiple and interconnected: parents may wish to spare their child a life that disability and/or disease would render excessively taxing. They may also suffer at the prospect of being helpless witnesses to their child's suffering.

Embryo selection in a PGD procedure, is seen by couples requesting it as the safest way of sparing their children the hardships which they themselves (and/or their own parents) endured. That parents wish to avoid having a second child with the same serious condition as an older sibling does not mean that they reject their older child's condition; it simply means that they wish to spare their second child that same hardship and organise the life of the family in the best interests of all its members, including the affected older child.

I.2.3. Can it be said that the purpose of antenatal diagnosis is "eugenic"?

In France, there are 800,000 births every year and some 6000 medically motivated terminations, which cannot be considered an insignificant number²⁴. Insistent claims are voiced that a eugenic policy is being implemented. The current bioethics law prohibits eugenics which it assimilates to a crime²⁵. Undeniably, the meaning of

²² Article 1 of law no 2002-303 dated March 4, 2002 on the rights of patients and the quality of the healthcare system: "solidarity with the disabled".

²³ Legally, speaking of prevention in a prenatal context would have far-reaching repercussions on the interpretation of Article L1131-1 of the Code of Public Health which recommends that relatives should be informed following the diagnosis of a serious genetic disorder "when preventive measures or treatment are possible". It should be noted that in its report on the implementation of the decree, ABM's "*Conseil d'Orientation*" (governing body) (Opinion 32 dated July 6, 2007) refused to pronounce itself on this point. "The Conseil d'Orientation wishes to make it clear that its Opinion only concerns serious genetic disorders present or at risk of being present in persons already born. The possibility of informing relatives for preventive measures before a pregnancy, using PND for example, requires extensive debate and further reflection to complement this Opinion".

²⁴ In 2005, 2006 and 2007, the number of certificates delivered for medically motivated terminations were respectively 6 441, 6 790 and 6 645 (cf. ABM activity reports : <http://www.agence-biomedecine.fr>).

²⁵ Eugenics is expressly condemned in Article 16-4 para. 2 of the *Code Civil*, which is public policy (art. 16-9). Article 214-1 of the *Code Pénal* (Criminal Law Code) denounces eugenic practices for the purpose of organising selective breeding

"eugenics" that legislators were referring to is an ideology for racial hygiene to further the improvement of the human species, formed into a political programme²⁶. Events in the last century have shown the potential for barbarity contained in biopolitical ambitions so seriously prejudicial to individual liberties. Today, healthcare professionals are not under any constraint by government instruction to persuade women into asking for therapeutic termination or embryo selection when there is a strong possibility that they may give birth to a child suffering from a severe and incurable disease. Providing objective information is the only obligation on the medical professions.

The ethical issue is how the medical professions and the public regard the obligation on physicians to inform every pregnant woman of the existence of a screening test for trisomy 21. The difference between the obligation to speak and encouragement to proceed is both fundamental and tenuous. We are aware that screening — or even diagnosis (once past the risk threshold) — is supported financially by the national sickness insurance system. Trisomy 21 is the object of a screening offer although there is no remedy or prevention (unless therapeutic termination is viewed as a means of prevention, which was discussed and disputed above).

The criterion for differentiating trisomy 21 screening (with medically-motivated termination consequences) from a eugenic policy is that none of its successive steps (screening, diagnosis, termination) are mandatory²⁷. Nor is there any obligation on couples. The offer of therapeutic termination if trisomy is diagnosed does not *encourage* termination, it simply *mentions* the possibility²⁸. There is no point in offending any feelings with talk of "eradicating" trisomy — or any other genetic disorder — as if it were an infectious disease. The frequency of questions asked on the subject of trisomy 21 is to be compared with the frequency of this chromosomal condition which is the most prevalent of foetal affections and causes of mental handicap.

On the one hand, antenatal examinations and tests are never neutral:

Monitoring pregnancies does not aim simply to reassure. It also serves to provide information on foetal health. When a woman undergoes the ultrasound scans at the prescribed intervals during pregnancy, even though she may not be explicitly aware of this, one of the reasons is that, should the case arise, she may terminate her pregnancy

punishable by a 30-year prison sentence. Cf. Articles 214-1 to 214-4 of the *Code Pénal*, "Ch. I: Eugenic and reproductive cloning crimes". Article 214-1 was added by Law n° 2004-800 of August 6, 2004, Art. 28 I, *Journal Officiel* dated August 7, 2004. "Implementing eugenic practices for the purpose of selective breeding is punishable by thirty years imprisonment and 7,500,000 Euros fine".

²⁶ Francis Galton, who supported this concept in the 19th century, saw eugenics as a way of reversing the "degradation of the human species" cf. Galton F., *Hereditary Genius. An Inquiry into its Laws and Consequences*. Gloucester Mass, Peter Smith, [1869], 1972; "Eugenics, its definition, scopes and limits" in *Sociological Papers*, Macmillan, 1905. For Galton and his followers, society should "foster judicious mating" so that individuals with remarkable characteristics would be encouraged to breed while those less genetically privileged could be advised against producing offspring.

²⁷ "Systematic" means "offered to all women".

²⁸ Note: there are other reasons for rejecting screening, such the health risk of a termination for the woman concerned.

if a severe and incurable anomaly is detected²⁹. There is no denying that terminating pregnancy is not an obligation, out of respect for autonomy. But full and entire autonomy corresponds to a personal initiative, as is the case for elective abortion by reason of emotional distress. However, in these particular circumstances, it is the doctor who detects an anomaly and raises the subject of termination. Practitioners tell us that many couples were unaware that termination was a possibility beyond the legal deadline for elective abortion.

On the other hand, individual decisions are conditional on social attitudes:

Leaving aside the influence exerted by the family, the frequent lack of solidarity, support and solicitude suffered by the disabled in our society does come to mind. Furthermore, for the majority of people today, it appears unreasonable to continue with a pregnancy when it is known fact that the child will be seriously impaired during the whole of its life. The normal course of action is seen as accepting amniocentesis in case of doubt, and termination if the diagnosis is negative. Such social and cultural difficulties may induce reluctant parents to choose abortion.

The competent authorities could move in favour of parents' freedom of choice by enhancing social representations of trisomy 21 disability. In recent years, the quality of life of those affected has been improved by better management. Without any intention of disputing the current screening system, nor of blaming in any way couples who do not wish to bring up a Down's syndrome child, CCNE considers that this progress is worth reporting to the public at large. Promoting continuing medical training on intellectual deficits would also be helpful in this respect.

Moreover, publicly funded research on trisomy mechanisms (biochemical effects linked to the presence of an extra chromosome) or on cognitive and psychological fields deserve to be encouraged, so as to improve the intellectual performance of people with trisomy 21. Generally speaking, any measure which contributes to improving the quality of life of people with mental handicaps complies with the demands of the law dated March 4, 2002 which stipulates that "all those affected by disability, irrespective of its cause, are entitled to the nation's solidarity".³⁰

II. Assessment of the severity and incurability of diagnosed diseases

²⁹ Quite frequently, it is when women are told that amniocentesis may be advisable that, retrospectively, they realise what is involved (on this point, see page 7 of this Opinion).

³⁰ Law n° 2002-303 dated March 4, 2002, on the subject of patients' rights and the quality of the healthcare system. II - "all those affected by disability, irrespective of its cause, are entitled to the nation's solidarity". www.assemblee-nationale.fr

When PND leads to the diagnosis of a foetal defect for which there is no possible preventive or curative remedy, parents and more specifically the mother, after discussion in an interview with the echographer, obstetrician or geneticist, may formulate a request for medically-motivated termination. Her request is then considered by a multidisciplinary centre for prenatal diagnosis (CPDPN) who will evaluate the severity and the incurability of the disorder and will deliver, if appropriate, a certificate authorising termination. If a familial genetic disorder is sufficiently severe and incurable for a PGD request to be granted, this will also be a decision by the CPDPN. One of the major ethical issues is to determine how severity can be evaluated.

II. 1. CPDPNs on the issue of severity

Severity is a concept which contains a tangible somatic dimension to which CPDPNs are justified in granting pride of place. A couple's personal representation of severity comes second, but is not secondary.

The situations encountered by CPDPN participants can be summed up as follows:

- Foetal developmental anomalies discovered by ultrasound (limb anomalies, dwarfism, etc.);
- High penetrance genetic disorders³¹ with quality of life consequences, some of which are early onset diseases (myopathies, spinal amyotrophies, cystic fibrosis) and others with later onset (Huntington's disease, some myopathies, etc.);
- Diseases with an impact on psychomotor development with repercussion on the life of the family and in society (trisomy 21, fragile X syndrome, some kinds of hydrocephalus);
- The presence of a high risk of children or young adults developing life-threatening diseases (certain hereditary cancers in children and young adults).

This typology shows how diverse are the areas of severity, with the need in each case for specific appreciation, with of course some degree of overlap. The various areas focus on the hardship likely to be endured by the future child.

Although it does contain an irreducibly objective dimension, the concept of severity also allows for degrees dependent on the attitudes of society, close relatives and future parents. While the determination of the degree of severity of the foetal anomaly is one of the CPDPN's primary tasks, the members of this multidisciplinary group must also integrate the non medical component of severity. Severity is associated with suffering. But since different people and different circumstances will give rise to different suffering, the difficulty confronting CPDPNs is to decide which foreseeable suffering should be included in their assessment. Although they are intimately connected, the expected suffering of the unborn child and the suffering of the couple concerned must be conceptually dissociated.

³¹ Presence or absence of expression of a gene carried by an individual. When 100% of the carriers of the gene express it in their phenotype, penetrance is said to be complete. For example, in achondroplasia, foetal penetrance is 100%.

II.2. The expected suffering of the unborn child

The moral impact suffered by the person concerned may be less marked in the case of a mental handicap than for other disabilities. The cause of distress is *awareness* of a visibly noticeable handicap when it is reflected in the eyes of others.

Mentally handicapped people, however, may be made more uncomfortable and more exposed to personal and corporal distress because they cannot express it. There are also cases when severity is not tied to the disability itself but to the consequential pathologies generated by the handicap (such as limited access to mobility).

With genetic diseases, CPDPN assessment of severity may be complicated by the variability of expression of the disorder. The future severity of a future child's condition is difficult to predict because of variable expressivity depending on factors which, still quite frequently, are not identified. For instance, in type 1 fibromatosis (NF1), expression of the disease may be no more than a few "café-au-lait" (light brown) spots or in more serious cases be associated with mental handicap or plexiform neurofibromas whose location may be the cause of severe skin injury and serious complications (cancerous tumours, in particular malignant growths on nerve sheaths). One of the four first full-face transplant operations performed in France concerned a young man with NF1³².

Exploring the family history (for the so-called "dominant" group of genetic disorders) can help CPDPNs to anticipate, to some extent, severity of impairment. It was this reference to the history of close relatives which led the authors of an "*Agence de la Biomédecine et de l'Institut national du cancer*" (INCa)³³ report to propose that certain hereditary forms of cancer affecting young adults could move CPDPNs to certify to the severity of a disorder and thereby accept the principle of a request for medically-motivated termination or PGD.

The severity of impairment a child will suffer is also connected to the quality of care and management he or she is likely to receive. This in turn is linked to the particular circumstances of each child's environment (the family's degree of cohesion, spiritual faith, moral and economic resources, etc.) but also to the quality of welcome into society that is available to a disabled child, and later to a disabled adult.

Clearly, the severity of an abnormality cannot simply be equated to a given society's capacity to integrate a disability. Even within a society where human solidarity is at the highest level, the severity of a handicap does not become a trivial matter, although society would become less humane if it lost sight of the effect it has on the perception of this severity.

³² One legal criterion is the high probability of the disease appearing. In fact, there are disorders for which statistics show that the probability is not very high, but not insignificant. Taking the example of isolated agenesis of the corpus callosum, 80% of children are unaffected by mental retardation and 20% are mentally retarded. Among those with no mental retardation, one third are capable of attending non-specialised schools but have specific learning disorders (dyslexia, attention deficits, slowness).

³³ "*Place du DPN, de l'IMG et du DPI dans les formes héréditaires de cancers*", (The role of prenatal diagnosis, medically-motivated termination and PGD) April 2008. www.e-cancer.fr ; <http://www.agence-biomedecine.fr>

The contextual and relational difficulties a child may encounter throughout life are parameters of severity to which the CPDPN can legitimately devote some time for debate when they meet to examine these cases. It is part of the CPDPN's mission to take account of the non medical aspects of severity, in addition to the severity they have previously and objectively assessed in the light of medical considerations.

That a severity assessment cannot dispense with the consideration of certain variables is sufficient in itself to justify the decision of legislators to abstain from listing the disorders for which a couple's request would be admissible (and indirectly the list of disorders for which such a request would be inadmissible). Since there is no list, CPDPNs can examine the circumstances on a case by case basis. It also means that discrimination against people affected by one of the diseases on such a list can be avoided.

II.3. The suffering of parents

In so far as a child's sufferings are closely connected to the relational context, CPDPNs are within their mandate in considering the sufferings of parents (or even of the rest of the family) when they deliver the severity certificate. In these trying situations, CPDPNs are faced with real sufferings, not imagined ones³⁴. It is appropriate to mention here that in the present circumstances, saying that parents are intent on the "perfect baby", or that they are keen on requesting termination at the mere suspicion of a minor anomaly, is simply inaccurate. In the immense majority of cases, parents just want to have children who are no more or less unwell than the average child.

The degree of suffering borne by parents at the prospect of having a severely sick child, depends on a number of personal circumstances: their faith, beliefs, cultural perceptions, fear that their child might survive them and of not knowing who would care for him in that event.

Although, however, there is good reason for considering parents' sufferings when the severity of the foetal disorder is assessed, this raises the question of whether society should give healthcarers the responsibility of certification decisions which include a non medical dimension. Should an appreciation of severity and incurability be left to the sole ministrations of CPDPNs? Should people who are able to register more personal and less medical views, such as the sufferings endured by parents, enter into the membership of CPDPNs?

It must be said on this point that the CPDPNs' multidisciplinary nature is not limited to the medical professions. Medical psychologists are already included in their composition and there are plans to include gradually expertise on genetic counselling. The Committee considers that adding too many actors, such as the views of civil society or

³⁴ Bouffard C, S Viville & BM Knoppers (2009), "Genetic diagnosis of embryos: Clear explanation, not rhetoric, is needed", *CMAJ*, 181: 387-91

of associations, would not be appropriate, mainly because the severity and incurability decisions are based on collegial debate supported by medical data and that parents' personal perception of severity and the sufferings they endure as a result of this perception, are also taken into account.

While parental sufferings at the prospect of giving birth to a seriously sick or handicapped child deserve to be heard and entered into the equation, there is also a need to take account of the distress generated by having to terminate pregnancy. The strength of the bond between mother and foetus is so great for a number of pregnant women that sometimes a medically motivated termination is more distressing even than the prospect of having a severely handicapped child. For this reason, even when scientific and medical circumstances would allow termination, parents (and more specifically mothers in this case) may take the decision to continue with the pregnancy.

What if, on the contrary, a distressed couple request termination for medical reasons and the CPDPN considers that the ailment is not severe and incurable? The fact that an unborn human being is no longer wanted is a serious reason for continuing to dialogue with a couple devastated at the thought of its birth. That CPDPNs should take account of the distress and reluctance of the parents is legitimate in that it is clear that a child with even a minor impairment will be needing the love of its parents to face up to life "with a difference". In such circumstances, there is always a danger that objectivity will be lost and compassion will add to the confusion. Such moral quandaries cannot be solved *a priori*. At present, they are not very common. The currently available feedback shows that in effect, there are but few "discrepancies" between CPDPN expert conclusions and the expectations of the couples concerned. In 2007, for example, only 112 certificates of severity were denied to requesting parents³⁵. Contrary to what might be expected, differences in appreciation between the parents and CPDPNs are more frequently on the side of continuing with pregnancy³⁶. Cases in which parents do not take up the possibility of medically-motivated termination (despite the severity of foetal impairment) is a clear sign that freedom of decision is in their hands and that it is not purely formal.

Medical practice has always included the subjective dimensions of suffering. There is therefore no more need in this case than in others to make the point of parental distress explicit in the text of the law. Emphasizing the parents' personal evaluation could in fact increase it rather than alleviate it, as it would also emphasize that their decision is a solitary process. The end result of such a change would be to shift responsibility from the CPDPN to the parents. The role of professionals involved in antenatal diagnosis is to help parents share the decision with them, not making them shoulder the full responsibility of it.

³⁵ See: ABM 2007 Progress Report. www.agence-biomedecine.fr

³⁶ During that same year, while 6,642 severity certificates authorising termination were delivered, 475 pregnancies continued nonetheless (i.e. 7% of the certificates), including serious anomalies leading to death during pregnancy or soon after birth in almost half of these cases.

In this connection, the Committee considers that in spite of the difficult problems raised by the burden of late termination, the current rule allowing termination at any time before term is, in the final analysis, preferable to setting a threshold. There are situations of uncertainty which require sufficient time to stop and make a well-considered and informed decision. The severity which is apparent through ultrasound examination at one point in a pregnancy may be attenuated as the child in gestation matures. Setting an absolute deadline for medically-motivated termination would lead to the obligation of hasty — and therefore more precarious — decisions.

III. PND and PGD: specificities and links

For some diseases, the distress suffered by parents who previously resigned themselves to medically motivated termination raises the issue of justification for access to PGD when they again wish to have a child. Should embryo selection be viewed as an alternative to medically motivated termination? Are other indications to be considered?

III.1. Embryo selection in connection with PGD cannot always be considered an alternative to medically motivated termination

Although it is listed in the Code of Public Health as one of the modalities of PND, PGD is not an ultra-early form of PND. Four points should be underlined in this connection:

a) All the disorders diagnosed by PND and leading to the offer of termination do not allow for later recourse to PGD. There are medical and scientific reasons for this: PGD can only be used for *genetic* (genic or chromosomal) diseases carried by at least one of the two parents, whereas PND concerns any disorder detectable *in utero*, using a variety of techniques, including ultrasound. A large proportion of medically motivated terminations are not connected to any genetic disorder, but to malformations determined by multiple causes.

b) PND concerns potentially all pregnancies *via* the offer of ultrasound screening and serum markers for all pregnant women. On the contrary, PGD arises in the context of personal or family case histories.

c) With PND, anomalies are detected once pregnancies are under way. PGD is an *ex utero* test, requiring assisted reproductive technology.

d) Finally, PND may have preventive or therapeutic relevance when it gives rise to medical management of a foetus or new born child, which can never be the case with PGD which involves selecting healthy embryos, free of the family disorder under exploration.

There are therefore significant differences between PND and PGD. Embryo selection in connection with PGD cannot be viewed as simply an alternative to medically motivated induced abortion, which is not specific to genetic foetal defects. The essential purpose of PGD is to avoid having recourse to the termination procedure — always a source of trauma — in the context of a severe hereditary defect. The Committee wishes to point out in this connection that there is no necessity for a woman to have had to suffer a previous medically motivated termination before allowing her to request PGD, providing there is a proven risk of transmitting a severe and incurable genetic disorder to the child. Nevertheless, although PGD does prevent emotional trauma, it is by no means painless. It requires a fairly elaborate and invasive procedure (ovarian stimulation and puncture, etc.). It is also a source of anxiety since at each stage of the procedure, there is a high risk of failure: the live birth success rate after oocyte retrieval is around 20% and there is little likelihood of this figure improving in years to come since it is in fact quite close to the figure for natural conception.

III.2. Ethical issues raised by progress in diagnostic techniques

III.2.1. Extending PGD?

CCNE considers that the only indisputably ethical purpose of PGD is to give parents the possibility of having a child in situations where family history or a severely handicapped firstborn would have induced them to abandon the project for fear of the high risk of transmitting a serious hereditary disorder. The current legislation's safeguards, such as severity and incurability criteria, need not be revised; they have been proved adequate as regards their capacity to regulate requests and practices. In other words, as regards genetic disorders, it is essential to reject the idea that a request for PGD could be sustainable if it would not be sustainable for medically motivated induced termination (as the current law provides). When there is a possibility of choosing either PND or PGD, the parents alone must take the decision once they have been properly informed.

The Committee considers however that forbidding screening for trisomy 21 while proceeding with PGD for a genetic disorder carried by one of the parents is a rule which needs to be reversed. The purpose of PGD is a pregnancy which, like any other, would be monitored and possibly followed by amniocentesis. PGD for trisomy 21 would only be considered insofar as it did not modify the conditions required for embryo biopsy and, in particular, an increase in the number of cells sampled, which would have the effect of reducing the number of live births³⁷. Certain members of the Committee do not agree with this proposal. They fear that this would lead to modifying substantively the practice of PGD by removing a limitation. Trisomy might not be the only malformation investigated and the procedure extended to all assisted reproductions. These members consider that the current prohibition charts a middle course which is worth retaining.

³⁷ De Vos *et al.* Impact of cleavage-stage embryo biopsy in view of PGD on human blastocyst implantation: a prospective cohort of single embryo transfers. *Human Reproduction*, September 2009

In the framework of a standard IVF procedure, however, for infertility and not motivated by a family history of genetic defects, CCNE has reservations regarding the possibility of screening for chromosomal anomalies before implantation in the uterus. This would be adding a step to the existing procedure, i.e. embryo biopsy. The possibility that screening for aneuploidy and eliminating affected embryos could improve the success score of IVF has been put forward. Independently of the cost such an approach³⁸ would generate, studies to date have not revealed any benefit as regards the number of at-term pregnancies. We should add that such an extension of PGD would weaken the most useful of the markers limiting the procedure set by the law: a diagnosis exclusively reserved for parents whose child runs a major risk of being born with a severe and incurable genetic disorder, in the light of the family history.

CCNE considers that PGD for the reason that the family's quality of life would be improved by the possibility of choosing the gender of their future child ("family balancing") is unacceptable. Such practices give rise to misgivings and reluctance because they reduce severity to the rank of subjective preferences, devoid of biological substance. The (supposed) interest of the parents is the sole concern. The child is cast in the role of a programmable object obeying orders. Similarly, PGD would not be acceptable for the reason that a child would have a better quality of life if he or she were endowed with the sensory characteristic that allows integration in a community (for example choosing to have children with gene-related deafness when both parents are also deaf). Using PGD for such purposes amounts to a form of medical misuse and biological manipulation.

The impossibility of demonstrating the long term harmlessness of all the steps in a PGD procedure constitutes a boundary which could contain the possible extensions of society's expectations. Once parents understand that expected benefits and risks incurred must be balanced, self-regulation of requests becomes a possibility. There are, on the one hand, *proven* risks in hyperstimulation and ovarian puncture and, on the other hand, *potential* risks in connection with the future of children conceived artificially.

III.2.2. PGD for therapeutic purposes

This is a very particular form of PGD: the "saviour baby" or, as some prefer to express it, the "designer baby"³⁹, specially "designed" to effect a cure. CCNE maintains the principle it defended in an earlier Opinion on this subject: "...making it possible for a baby the family wishes to have anyway, to represent - also - a ray of hope of a cure for

³⁸ In 2007 in France, 52,334 IVF procedures were attempted (<http://www.agence-biomedecine.fr>). Even if PGD for trisomy 21 were to be offered solely to women of at least 38 years of age, such numbers would completely overwhelm the PGD centres. Only 244 oocyte punctures were performed with a view to PGD during that same year. Furthermore, the financial cost would be enormous.

³⁹ In this case, PGD is performed for a couple with a child with a genetic disorder for whom hematopoietic cells taken from umbilical cord blood need to be transplanted. The sick child's ailment may be Fanconi's syndrome, drepanocytosis or some of the more severe forms of anaemia. Embryos are selected twice over: for the absence of the genetic defect concerned and for HLA tissue compatibility with the ailing child. All such requests are reviewed by the Biomedicine Agency.

the older sibling, is an acceptable objective, albeit not the prime objective⁴⁰. As the law currently provides⁴¹, this extreme possibility should be reserved entirely for couples with a child suffering from a life-threatening disease. The ailing child's life expectancy must be significantly improvable by therapy which does not impair the integrity of the new sibling whose birth is consecutive to a PGD procedure.

Great care must be taken to avoid the risk of a child conceived in such circumstances becoming a commodity. Thought must be given to the burden that child would bear, in particular if the transplantation fails⁴². Parents must be counselled to help them anticipate the possible psychological repercussions for their future child.

CCNE wishes to draw attention to the fact that increased technical feasibility⁴³ could do no more than mitigate the magnitude of the ethical issue. PGD's *aim* may be therapeutic for the benefit of a third party, but cannot be in itself *stricto sensu* a "therapy"⁴⁴. A child is never a medication. Even if it were improved, the technique should still be a "last resort". One can only hope that it will only be used temporarily and that active research will produce an alternative. The development of cordon blood banks would seem to be the most promising solution at this time⁴⁵.

⁴⁰ The National Consultative Ethics Committee Opinion n° 72, July 2002

⁴¹ Since 2004, the law - article L. 2131-4-1 of the Code of Public Health - allows PGD conception for the purpose of transplantation to treat an older sibling born with a genetic defect, on the condition that the child's integrity is not violated.

⁴² Cf. Bayle B. *L'embryon sur le divan, psychopathologie de la conception humaine*. Collection « Médecine et Psychothérapie », Masson, Paris, 2003

⁴³ Note: the operation has met with only limited success so far and this will probably continue to be the case in the medium or even in the long term. Additional to the PGD failure rate (embryo biopsy, small number of live births after embryo transfer) must be added the small number of embryos which are both disease-free and HLA compatible.

⁴⁴ At this point, inclusion in the law of this possibility is only experimental.

⁴⁵ Cf. The National Consultative Ethics Committee Opinion n° 74 "**Umbilical Cord Blood Banks for Autologous Use or for Research**" (<http://www.ccne-ethique.fr>)

See also the French Senate's report n° 79, on behalf of the Social Affairs Commission, on the therapeutic potential of umbilical cord blood stem cells, by Marie-Thérèse Hermange.

IV. Prospective analysis

IV.1 Is it acceptable to screen the population at large to identify couples at risk of giving birth to a child with a severe and incurable disease?

Today, one of the circumstances leading to using PND (and medically motivated induced termination in the event of a foetal defect) or PGD, is knowing of the existence of a family history of genetic disease and of one or several mutations which cause it, depending on whether the mode of transmission is dominant or recessive. The reason why such circumstances have remained linked to family history is that these are rare disorders and they are frequently associated with a wide diversity of mutations.

In certain populations, frequent and serious genetic disorders, with a small diversity of mutations, reflecting a founder effect⁴⁶, have been the reason for launching identification campaigns targeting risk couples. Some examples are thalassemia in Sardinia and Cyprus and Tay-Sachs disease among persons of Ashkenazi descent. It may be possible that the higher expertise in genetic testing acquired in recent years could lead to extending these identification campaigns to couples at risk for severe genetic disorders, regardless of founder mutations or the presence of a family history. The recent recommendations of the American College of Medical Genetics (ACMG) on the subject of spinal amyotrophy would seem to indicate a move this direction. Transmission is recessive with one single mutation representing 95% of mutations. One person in 40 is a carrier for this mutation in the American population. ACMG recommends that screening for this mutation be offered to all couples wanting to start a family and to all pregnant women.

In France, this kind of issue arises more specifically in the context of long term consequences of neonatal screening for cystic fibrosis. There is a possibility that a similar policy could be recommended⁴⁷. Screening for cystic fibrosis results in an increase of the number of couples identified as being at risk by genetic testing performed in families after one affected child – or even only a heterozygote carrier of the CFTR mutation – has been identified. CCNE has already considered this question of identification within the general population of couples at risk for cystic fibrosis⁴⁸ in its Opinion n° 83 in 2003. The Committee had expressed at the time some misgivings concerning a generalisation of such pre-conception screening and the Committee still

⁴⁶ Founder effect: Major changes in the allele frequency of a new population formed when a small number of individuals splinter off from a parent-population. More often than not, there occurs a reduction in genetic diversity in the new population compared to the original population. In some populations, a mutation is responsible for most cases of a given hereditary disease. The founder effect may be the reason for this situation: one ancestor carries a mutation (a new mutation or migration of a carrier) which is then passed on to following generations. A founder effect is all the easier to observe when the new colony is small and its composition has not changed very much over time, so that it is mostly to be found in genetically isolated populations, be the isolation geographic or cultural in nature.

⁴⁷ The National Consultative Ethics Committee Opinion n° 97: Ethical issues arising out of the delivery of neonatal genetic information after screening for genetic disorders (the examples of cystic fibrosis and sickle-cell disease) www.ccne-ethique.fr

⁴⁸ The National Consultative Ethics Committee Opinion N°83: Generalised prenatal screening for cystic fibrosis. www.ccne-ethique.fr

has the same reservations because of uncertainty on the severity of expression of the disease. While it is true that a large number of children carrying two (inactivating) mutations of the CFTR⁴⁹ gene will be seriously affected with major repercussions on their quality of life and a shorter life expectancy, for others the disease will take a milder form and be compatible with a normal or quasi-normal life style. The variations in the condition's expression are caused by the existence of both genetic and non genetic factors, and the greater number of these modifiers remain to be identified. In the circumstances, while it is reasonable to take account of the severity of expression of the disease among close relatives, extreme caution must be exercised regarding an assessment of severity when there is no family history of the disease. There is currently a risk of over estimating severity.

Whenever generalising identification of at risk couples *via* the identification of gene mutations is under consideration, the central issue must always be the predictive value of such mutations in terms of severity and incurability. Today, this issue stands in the way of rapid generalisation of such tests.

IV.2. Ethical issues in connection with the prospect of ultra-early antenatal diagnosis

New ethical issues may arise out of the combination of several parameters:

- accessibility of foetal DNA circulating in the blood of pregnant women,
- the generation of genetic markers for which clinical validity is not always proven,
- these tests being available on the internet *via* commercial offers⁵⁰.

The indisputable advantage of access to this ultra-early information without intra-uterine retrieval is that it avoids using invasive and risky processes (amniocentesis, etc.). But the corresponding drawback is the risk of proceeding with elective termination at the slightest doubt (before the legal deadline) for couples who are left to their own devices. The danger resides in the speed of diagnosis which does not give couples enough time to think the matter through. With screening and diagnosis forthcoming all at once, ultra-early tests could short-circuit time for decision. The decision to pursue or terminate pregnancy would no longer be the results of a thought process but perhaps more like an instantaneous reaction. In such circumstances, counselling provided for the mother should be even more careful.

- The prospect of PND based on the pregnant woman's blood also seems likely to foster anxiety for couples who will be getting the results of genetic testing within the legal 14 weeks of amenorrhoea, i.e. the limit for elective termination. Indeed, the study of foetal cells that can be sampled in the mother's blood and "probabilistic" nature of the data provided by genetic tests may well lead to a number of misgivings due to prognostic

⁴⁹ The CFTR gene ("Cystic fibrosis transmembrane conductance regulator") provides the code for a cell membrane protein. Mutations of the CFTR gene are the cause of cystic fibrosis.

⁵⁰ Private companies accessible via the internet could make available sophisticated genetic tests (such as "pangenomic chip screening for deletions and duplications"; SNP chips with 600,000 variations; complete sequencing of the coding region of genes).

uncertainty. Having obtained information without medical assistance, how will couples deal with the predispositions of a child in gestation for the development of a disease of which their knowledge is only incomplete? It is to be feared that predictive medicine when it concerns the embryo will be mainly focusing on predispositions for late-onset diseases. If results of the test are available quite rapidly and perceived as threatening, the couple could choose to terminate although a CPDPN would have rejected the request.

- If such tests were available through private agents selling their technology electronically, couples might well choose to act without any appropriate medical assistance or moderating external advice. There would then be a real threat of predictive "medical tourism" becoming the norm with helpless and distraught couples attempting to cope with unvalidated test procedures.

- Finally, there could be a confidentiality issue regarding the biological privacy of a third party (future child or indirectly, spouse) in the event that offers based on a full genome exploration were to become more commonplace.

There is no other way of avoiding such unwelcome developments than providing information pedagogically through institutional channels. Harmonising legislation on an international scale is a hazardous undertaking due to cultural particularities (see for example the differences between countries as regards paternity tests), even though we should try to move in that direction at the European level. What really needs to be done is help couples to acquire genetic knowledge, to become aware of the limitations of such knowledge, of the risks of excessive diagnosis and, at an absurd extreme, of the risk of never conceiving a child. It must be remembered that no human being is born genetically exempt of the risk of developing a serious disease at some point in his or her life.

Conclusions and recommendations

CCNE considers that the articles in the law on bioethics concerning prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) are a generally satisfactory legal framework and do not require any major reappraisal. The safeguards provided by legislators are sufficient to prevent unwelcome "slippery slope" developments.

Some of the existing provisions deserve the full attention of those in charge of their implementation, such as the way in which information is given to couples and the rules of good practices as regards screening and diagnosis of chromosomal anomalies which could reduce the risk of miscarriage due to foetal sampling.

While PND can lead to avoiding the birth of children with severe and incurable diseases, it is essential that the therapeutic objective continues to be specifically included in the law in every case of curable pathologies for which medical treatment is available for foetuses or newborns.

CCNE emphasises that for couples to have a free choice, the country's duty of solidarity for the disabled stated in the March 4, 2002 law must be respected.

Ethical concerns regarding the assessment of the degree of seriousness of diseases are addressed in current legislation:

1) Procedure in the multidisciplinary centres for prenatal diagnosis (CPDPNs) allows for determination of the degree of severity and incurability of the disorders (the objective determination being in the hands of medical expertise) to be tempered, for humane reasons, by taking into consideration the couple's perception of the seriousness of the situation and the distress it may cause them.

This is the context in which families with a history of hereditary cancers could be cared for. CCNE recommends on this point that a distinction should be made between, on the one hand, simple multifactorial susceptibility and, on the other, a genetic predisposition following monogenic laws of transmission and associated to a major risk of early-onset cancers, for which there are very limited treatment or prevention options. The severity of a disorder, and neither its origin nor its nature, are important to determine whether requests — both for PND and for PGD — are receivable.

CCNE did not support the idea of drawing up a list of disorders eligible for antenatal diagnosis. Even assuming the list would only be indicative, in the long term it could well become normative. A standardised procure would replace case by case analysis. It would be a constraint for the medical professions and discriminate against people with

these disorders. Nor is CCNE in favour of having people representing civil society participating in CPDPN deliberations.

CCNE points out that the reason for accepting a PGD procedure is the high risk of transmitting a severe and incurable genetic disease to a child, excepting any other implicit condition such as the fact that the women concerned, has or has not already undergone medically-motivated induced termination. In other words, if there is a possible choice between PND and PGD, the decision is in the sole hands of the couple concerned, once they have been properly informed.

2) Restrictions on access to diagnosis should be maintained. There does not seem to be a case for reversing the modifications that the law dated August 6th 2004 enacted, relaxing the PGD procedure (exclusion diagnosis and double PGD).

The right not to know — which must be respected for everyone without exception — justifies the so-called "exclusion" diagnosis so that a couple, of which one parent belongs to a family with a history of, in particular, late-onset neurodegenerative disease, can give birth to a healthy child without knowing whether the parent concerned is affected.

In the case of IVF because of infertility and not because of a family history of genetic defects before proceeding with PGD, CCNE recommends that the existing restriction be retained and refraining from carrying out embryo biopsy in search of an abnormality. However, while continuing to reserve PGD for couples with a family history, CCNE recommends lifting the current prohibition on screening for trisomy 21 before transferring the embryos which are not affected by the abnormality under investigation, so as to avoid the risk of trisomy being discovered during gestation.

CCNE recommends making certain terminological modifications to the law for symbolic purposes: removing the word "prevention" which is only partially appropriate to the aims of antenatal diagnosis. This extended use of the concept of "prevention" in the present Code of Public Health is on a par with telling people being tested to inform their relatives of the risks weighing on an unborn child.

Apart from legislative matters, CCNE recommends measures which could improve current practice:

- Provide support for PGD Centres confronted with receivable requests to which they cannot respond within a reasonable time frame;
- Analyse cases of disagreement between parental requests and CPDPNs;
- Encourage prospective research on the progress of children with malformations so that difficult decisions may be better informed.
- Collecting medical, sociological and psychological data on the quality of life of parents and children conceived following the use of diagnostic techniques would also help to gain a better understanding of their impact.

CCNE considers it would be useful for society to prepare for a better informed assessment of three risks in the future:

- The risk of falling into the lure of preferring antenatal elimination to seeking out ways of curing diseases. If the authorities were to promote and finance research on the subject, this would be an alternative to pseudo-preventive excesses that can only lead to strengthening stigmatising perceptions of people with a disability.
- The risk of an increase in the number of anxiety generating situations, of unconsidered and inappropriate terminations following on progress in diagnosis techniques and identification at a very early stage in the embryo of a large number of markers for susceptibility to frequent diseases. The early diagnosis based on a pregnant women's blood, although it does have the advantage of avoiding foetal loss induced by sampling, presents a risk of encouraging hasty decisions which may later be regretted by those who took them on the basis of incomplete data. The prospect of a development of commercial offers on an international scale for clinically unvalidated genetic tests should also be anticipated.
- The risk in connection with the loss of confidentiality of biological data relating to a third party (future child or indirectly, spouse) could increase with an extension of pangenomic investigations exploring multiple genes. Information could be disclosed which is not of any direct benefit to the health of the child concerned.

Not all ethical issues related to advances in diagnostic techniques can be solved by lawmaking, in particular when there is a globalisation of exchanges and services. The challenges which must be met require reflection on the genetic sciences, their culture, their learning and their democratisation. This effort to raise awareness could be developed, for the purpose of anticipation, in schools. Future generations would also benefit from a better understanding of the relational and social dimensions of handicap.

Paris, October 15, 2009