Belgian Advisory Committee on Bioethics

Opinion no. 49 of 20 April 2009
on the use of preimplantation genetic diagnosis (PGD) to detect healthy carriers of a mutation causing a severe hereditary disease for which offspring can have an increased risk

Request for an opinion of 19 March 2008,
from Prof. Dr R. Rubens, President of the Medical Ethics Committee of the UZ Ghent

Final version

CONTENT OF THE OPINION

Question put to the committee

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In a letter dated 19 March 2008, Doctor Rubens, President of the Medical Ethics Committee of the Ghent University Hospital requested an opinion from the Belgian Advisory Committee on Bioethics on the following question:

'[…] *As an ethics committee, we have been recently informed, via the "Center for Medical Genetics" of the Ghent University Hospital of a request for "preimplantation diagnosis aiming to avoid descendants being carriers of a severe genetic disease".*

In this case, it is a man suffering from X-linked recessive agammaglobulinemia (Bruton's Disease, MIM #300755). This disease requires life-long treatment with gamma globulins in order to improve resistance to infections. The sons of an affected man can never have the mutation (they will receive the X chromosome from the mother), but all daughters will be obligate carriers (they will receive the X chromosome from the mother and the X chromosome from the affected father).

The children of the couple that submitted the request will not develop the disease. Their daughters will later on present a 25% risk, for each pregnancy, of giving birth to an affected child (i.e. son). The couple asks for only male embryos to be selected via preimplantation genetic diagnosis (PGD).

The Medical Ethics Committee of the Ghent University Hospital handed down a negative opinion for this request, based mainly on the following reasons:

- *"a legal reserve, since the legislator targeted, when it spoke of 'sex-linked diseases' a severe disease that is directly communicable and not the fact of being a carrier of this disease";*
- *"the means currently implemented are limited";*
- *"other solutions will be proposed later to the daughters concerned (for example, a prenatal examination)".*

1. Demarcation of the opinion

This opinion only concerns asymptomatic carriers of a mutation causing a severe genetic disease (autosomal recessive* or X-linked recessive*)[1]. These carriers will now be referred to in the opinion by the more common expression "healthy carriers". "Healthy carriers" are therefore people who have the genetic mutation, but are neither symptomatic of nor affected with this specific disease or will not be in the future. In the case of an X-linked recessive disease (see explanation in point 2), girls carrying the mutation do not generally develop the disease. They may however present symptoms of it which will be less severe than those developed by boys who carry the mutation.

This opinion will therefore deal with the use of preimplantation genetic diagnosis (PGD)

[1] The words followed by an asterisks "*" are defined in the glossary *in fine*.
Further information on genetic diseases, genetic risks and genetic testing is provided in the brochure "Gènes, Générations et Société" published by the Centre for Human Genetics of the K.U. Leuven and is available in the book of the Advisory Committee on Bioethics entitled "Hérédité: tests génétiques et société", published by De Boeck-University (2001, pp. 119-135). An updated version of this brochure is also available in Dutch from the Centre for Human Genetics of the K.U. Leuven (VIB, 2007, achtste druk, herziene uitgave):
www.vib.be/NR/rdonlyres/A31D1C99-13A2-4DE1-BFFA-15CC510A46EC/2705/Aangenenzijde2008FINAAL.pdf

a. when the couple makes use of ART for fertility problems and, risking giving birth to a child affected with a severe hereditary disease, wishes concomitantly to avoid the birth of a healthy carrier descendant;

b. when the couple does not have fertility problems but, risking giving birth to a child affected with an X-linked severe disease, makes use of PGD and wishes concomitantly to avoid the transfer of healthy carrier embryos. Two situations are distinguished:
   1. the man is healthy and the woman is a healthy carrier of an X-linked disease: the male embryos have a 50% risk of being affected and the female embryos have a 50% of being healthy carriers of the disease;
   2. the man suffers from an X-linked disease and the woman is a healthy carrier of this disease: 50% of the male embryos will be healthy and 50% will be infected, whereas 50% of the female embryos will be healthy carriers and 50% will be affected;

c. when the couple does not have fertility problems but asks to make use of PGD to avoid the transfer of female embryos that are healthy carriers of a mutation causing an X-linked severe disease. This is the case when the man suffers from an X-linked disease and the woman is healthy and not a carrier (situation evoked in the question put to the committee): all the embryos will be healthy, and the female embryos will all be healthy carriers of the disorder;

d. the couple wishes to make use of PGD so that its child is not a healthy carrier of a mutation causing a specific autosomal recessive disease. When both parents are healthy carriers of the same autosomal recessive disease, 4 types of embryos may be obtained: 1 in 4 is healthy and not a carrier, 1 in 4 is affected (has inherited the mutated gene from the father and the mother) and 2 in 4 are embryos which carry either the mutated gene of the mother, or the mutated gene of the father, i.e. healthy carrier embryos. If a child is born from such a healthy carrier embryo, at adult age he or she will run a low risk (about 1 in 20 for frequent recessive diseases, such as mucoviscidosis) of meeting a partner also carrying a mutation in the same disease gene.

2. Preimplantation genetic diagnosis: procedure and indications

2.1. Introduction

Preimplantation genetic diagnosis or PGD enables the selection of an embryo obtained by *in vitro* fertilisation (IVF) and deprived of certain genetic anomalies before being transferred into the uterus. One or two cells from the embryo are generally taken for this purpose (embryo biopsy*), but other techniques - the taking of a polar body*, for example - may be implemented. This always relates to the targeted detection of a very specific mutation targeting persons with a high risk of transmitting the disorder to their children. Hence, although the genetic diseases resulting from a deficiency or a mutation in a specific gene or from a chromosomal anomaly are rare, they are generally accompanied by a high recurrence risk ranging from approximately 10 to 50%. Mucoviscidosis, for example, a genetic disease of the lungs and the digestive system, affects 1 in every 2,500 new born babies. After the birth of a first child affected by this disease, the recurrence risk is 1 in 4, i.e. 25%, for each child who follows, as for any *autosomal recessive disease**.

In women carrying an *X-linked disease**, the risk of having an affected children is 25%: 1 in 4 children is an affected boy, 1 in 4 children is a healthy boy, 1 in 4 children is a healthy,

non-carrier girl and 1 in 4 children is a carrier girl. If the man is affected by an X-linked disease, all his daughters will carry the mutation and all boys will be healthy. The girls carrying the mutation are generally healthy ("healthy carriers"), but in a certain number of X-linked diseases, they may also present symptoms, as in the case of *Fragile X Syndrome**. These symptoms are less frequently present in boys and are generally not as pronounced.

We will not take into consideration the genetic diseases where the carrier children themselves risk presenting debilitating symptoms, insofar as we consider that their situation is similar to that of affected children and is therefore distinguished from that of healthy carriers.

In most cases, there is no effective treatment against a number of hereditary diseases. Hence, the future parents often attempt to avoid the disease in the future child. In Belgium, there are eight centers for medical genetic to which interested parties can ask questions relating to hereditary diseases. They will gather information on the evolution of the disease, the treatment and follow-up possibilities, the recurrence risks and the possibilities of avoiding the transmission of the disease. These possibilities include, *inter alia*, the decision not to have biological children, to detect the disease during pregnancy and, where appropriate, to undergo an abortion, or make use of PGD.
PGD was performed for the first time in 1990, in the United Kingdom, thanks to new developments in reproductive medicine and genetics, in order to enable the birth of a child after sex selection based on an X-linked disease[2].

To be able to offer PGD for a given genetic disease, embryos must be obtained from *in vitro* fertilisation, there must be the technology required to carry out an embryo biopsy and specific knowledge about the chromosomal or molecular defect. Specific technical competencies are also required in order to detect a genetic defect in a single cell. The fluorescent in situ hybridisation (or FISH*) technique is mainly used to detect chromosomal anomalies, whereas polymerase chain reaction (PCR*) enables a specific genetic defect to be detected at DNA level.

It was in 1993 that the first baby was born further to PGD in Belgium thanks to the combination of the know-how of the Centre for Medical Genetics and the Centre for Reproductive Medicine of the UZ Brussels. The technique is now widespread throughout the world and one also has use of the selection of embryos to increase the chances of success of IVF[3].
The ESHRE consortium or "European Society of Human Reproduction and Embryology" reports around 3,000 children born after an embryo biopsy in Europe and in several centres throughout the world[4]. The follow-up studies carried out on these children have not been

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[2] Handyside A.H., Kontogianni E.H., Hardy K., Winston R.M.L., "Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification", *Nature*, 19 April 1990, 344, 6268, pp. 768-770.

[3] Within the framework of a preimplantation genetic diagnosis, the tests relate to a certain number of numerical anomalies of the chromosomal map and check if there is no significantly increased risk of developing a given chromosomal anomaly.

[4] Sermon K.D., Michiels A., Harton G., *et al.*, "ESHRE PGD [Preimplantation genetic diagnosis] Consortium data collection VI: cycles from January to December 2003 with pregnancy follow-up to October 2004", *Human Reproduction*, February 2007, 22(2), pp. 323-336; Andersen A.N., Goossens V., Gianaroli L., *et al.*, "Assisted reproductive technology in Europe, 2003. Results generated from European registers by ESHRE", *Human Reproduction*, June 2007, 22(6), pp. 1513-1525; Harper J.C., de Die-Smulders C., Goosens V., *et al.*, "ESHRE PGD Consortium data collection VII: cycles from January to December 2004 with pregnancy follow-up to October 2005", *Human Reproduction*, April 2008, 23(4), pp. 741-755; Goossens V., Harton G. , Moutou C. *et al.*, "ESHRE PGD Consortium data collection VIII: cycles from January to December 2005 with pregnancy follow-up to October 2005 ", *Human Reproduction*, December 2008, 23(12), pp. 2629-2645.

able to reveal, in the current state of scientific knowledge, any obvious difference in terms of congenital anomalies, birth or growth parameters up to the age of 2, compared to children born further to other ARTtechnologies.
In Belgium, approximately 1,000 babies were born further to an embryo biopsy between 1993 and 2008.

2.2. Procedure

PGD is a complex procedure, both for the couple and for the multidisciplinary team which is responsible for the PGD. The cost for society is very high. The UZ Brussels, in the last 15 years, has developed PGD for approximately 120 monogenic diseases.

The implementation of a PGD starts with a preliminary interview which takes place in a centre for medical genetics. This interview consists of checking whether the indication is medically correct and ethically acceptable (see point 4. Ethical considerations) and whether a PGD is technically possible. The procedure is explained and commented on, emphasising the complexity of the treatment, the relatively low IVF success rate, the existence of a low risk of erroneous diagnosis and the interest of a follow-up plan for babies born after PGD. The next stage consists of an information meeting and an examination at the centre for reproductive medicine to assess the chances of success depending on the potential fertility problem.

At the end of this information meeting, if the patients opt for PGD, the necessary preliminary examinations will be performed - mainly the taking of blood samples in order to prepare the genetic diagnosis. These preliminary PGD examinations may be more or less complex, depending on whether the couple is using existing procedures (for frequent diseases such as mucoviscidosis, for example) or not (if a new test has to be developed for an individual mutation associated with an extremely rare disease). A number of hereditary diseases are in fact due to a "private" mutation by family, such that the molecular research work based on the mutation is demanding in terms of intensity of labour and requires individual development for PGD.

Once the PGD procedure is ready, the patients can start a treatment cycle of approximately 6 weeks. The patients have to undergo an ovarian stimulation cycle enabling about a dozen mature eggs on average to be obtained. On day zero, the eggs are inseminated by intra-cytoplasmic sperm injection (ICSI) (only a single sperm is injected into each egg). About 7 out of 10 eggs are fertilised. In general 5 out of 7 embryos continue to develop to the stage of four cells on the second day and to the stage of eight cells on the third day. At this time, two cells (blastomeres) are taken as samples in view of genetic diagnosis. On the fifth day, 1 or 2 selected embryos are transferred. The potential normal supernumerary embryos are cryopreserved and will be eventually transferred later on when the couple so wishes.

2.3. Medical indications and personal motifs

Requests for PGD have increased over time and PGD is now an option for couples who present a high risk of giving birth to a child affected with a severe hereditary disease for which the mutation can be detected. PGD enables the transfer of only non-affected embryos. PGD can be used within the framework of an X-linked severe disease when the mutation is known. When the basis of the X-linked disease is not known, PGD enables, thanks to sex selection, only female embryos to be transferred. Couples who have difficulties with the notion of abortion, more willingly opt for PGD.

When the future parents are faced with a two-fold problem - fertility and genetics - the use of PGD seems obvious for those who wish to avoid the birth of a child affected with a severe hereditary disease. In this case, it is essential for the future parents to be directed towards a centre for genetic medicine in order to gather all information necessary and the appropriate counselling concerning their situation. Some people, carriers of an X-linked disease, may, during an *in vitro* fertilisation cycle, ask that the embryos that are healthy carriers of the mutation are not transferred. Only the embryos in which the absence of the mutation has been proved will be selected. In this case, account must also be taken however of their morphological quality and it is possible that only healthy carrier embryos have the quality required to be transferred.

Future parents regularly submit new requests. Hence, some parents, who have no fertility problems, may wish to make use of PGD solely to avoid the transfer of healthy carriers (see the question put to the committee where there is no risk of giving birth to an affected child since only the father is the carrier of the mutation).

3. Legal framework

From a medico-ethical standpoint, it would up to this point seem generally accepted that PGD is only authorised if there is a *properly medical purpose*, in the sense that the purpose is to transfer a healthy embryo to avoid the birth of a *sick or handicapped* child[5]. At a strictly legal level, none of the applicable texts enable a definitive answer to be given to the question of knowing whether the use of PGD is authorised or admissible in view of avoiding the birth of a child who is a *healthy carrier* of a severe genetic disease, rather than *affected with* this disease, on the understanding that the circumstance that this disease is sex-linked appears secondary. It is however fitting to summarise the legal sources available to date, by limiting the explanation of rules related to *indications* in view of which PGD is authorised, particularly from the point of view of the distinction to be made between the healthy carrier and the affected person, excluding other questions raised by this technique.

3.1. General principles / Supranational standards

Article 12 of the **Convention on Human Rights and Biomedicine**[6] provides, in a wide manner, that tests which are predictive of genetic diseases or which serve either to identify the subject as a *carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease* may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling. Article 14 adds that the use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where severe hereditary sex-related disease is to be avoided.

[5] In literature, see not. Florentin I., "Le diagnostic préimplantatoire et le contrôle de la qualité des enfants à naître", in Labrusse-Riou C. (dir.), *Le droit saisi par la biologie*, LGDJ, 1996, p.109; Gavarini L., "Experts et législateurs de la normalité de l'être humain: vers un eugénisme discret", in Testart J. (dir.), *Le magasin des enfants*, Gallimard, Folio/Actuel, 1994, p. 217; Mathieu B., "Force et faiblesse des droits fondamentaux comme instruments du droit de la bioéthique: le principe de dignité et les interventions sur le génome humain", *RFDpubl.*, 1999, p. 93.

[6] "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine", adopted by the Council of Europe in Oviedo, on 4 April 1997, but not signed by Belgium. See also, previously, Principles no. 5 and 17 stated (in 1989) in the report of the *ad hoc* committee of experts on the progress of biomedical sciences of the Council of Europe.

The **Universal Declaration on the Human Genome and Human Rights**, adopted by UNESCO on 11 November 1997, only comprises very general principles, thus the one according to which "research, treatment or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law" (Art. 5, a). Under the section "Research on the Human Genome", it is provided, on the one hand, that no research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people (Art. 10) and, on the other hand, that benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual. Freedom of research, which is necessary for the progress of knowledge, is part of freedom of thought. The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer *relief from suffering and improve the health of individuals and humankind as a whole* (Art. 12).

We will finally observe that the **Universal Declaration on Bioethics and Human Rights** adopted by UNESCO on 19 October 2005 comprises no provision specifically related to medically assisted procreation (MAP) or PGD[7].

3.2. Belgian positive law

The **Law of 11 May 2003 on research into *in vitro* embryos**[8] lays down the conditions to which these researches are subjected (Art. 3) and the limits to be respected (Art. 5). To this end, it recommends in particular research or treatments "*of a eugenics nature, i.e. based on the selection or amplification of non-pathological genetic characteristics of the human species*" or "*based on sex-selection, with the exception of selection which permits embryos affected with sex-related diseases to be set aside*" (Art. 5.4 and Art. 5.5). The law stresses the importance of free and informed consent of the persons concerned in the use of gametes or *in vitro* embryos for research purposes, after they have been given all the necessary information concerning the provisions of the law, the technique for obtaining the gametes, the *objective*, the methodology and the duration of the research or treatment (Art. 8).

In its opinion no. 33 of 7 November 2005 on somatic or germinal genetic modifications for therapeutic and/or meliorative purposes (pp. 9-10), the Committee considered that it clearly emerged from the preparatory works of this law[9] that, with regards interventions on the human genome, the legislator had intended to make a distinction between "germinal treatment" tending to improve the human species, which must be prohibited, and "corrective germinal treatment" tending to fight against a series of diseases such as Huntington's Disease, mucoviscidosis, haemophilia and various neuro-degenerative diseases, which is permitted. According to this opinion, the Belgian legislator considered that the germinal treatment techniques acting on a line of gametes of a living being could enable these

[7] The opinion no. 12 of the European Group on Ethics in Science and New Technologies of 23 November 1998 on ethical aspects of research involving the use of human embryos, does not, further, provide any specific information as to the medical indications justifying the use of PGD.

[8] *Belgian Official Gazette*, 28 May 2003; commentaries: Denies N., *J.T.*, 2003, p. 693; Leleu Y.-H., *R.T.D.F.*, 2003, p. 715. The Royal Decree of 15 February 1999 setting down the standards which "reproductive medicine" treatment programmes must respect in order to be approved (*Belgian Official Gazette*, 25 March 1999) does not, for its part, provide any relevant legal or ethical indication.

[9] Developments of the bill filed by Messrs. Monfils and Mahoux, *Parl. doc.*, *Senate,* 2000-2001, no. 2-695.

diseases to be overcome for the patient and *his or her descendants* and that this is therefore a therapeutic objective within the meaning of Article 3 of the Belgian Law of 11 May 2003.

These principles are reproduced in the Belgian **Law of 6 July 2007 on medically assisted procreation** and the destination of supernumerary embryos and gametes[10]. This law emerges from a bill filed with the Senate on 23 November 2005 which was, together with various texts related to surrogacy or surrogate mothers, the subject of an opinion of the Council of State on 14 February 2006 specifically concerning the compatibility of MAP, its consequences and the rules aiming to supervise it with the superior standards and fundamental rights applicable. At the end of quality consideration work, mainly in the Senate, the text was adopted in the Senate on 15 June 2006 and in the House of Representatives on 15 March 2007[11]. The law defines preimplantation genetic diagnosis widely as the "technique consisting, within the framework of *in vitro* fertilisation, of analysing one or more of the genetic characteristics of *in vitro* embryos in order to collect information which will be used to select the embryos which will be implanted" (Art. 2b) and sanctions it in its Articles 66 to 72 constituting Section VI.

After "*accurate information*" on PGD has been provided by the fertilisation centre consulted by the author or authors of the parental plan (Art. 66) an *agreement* is drawn up between them, which expressly mentions the agreement of the author(s) to the carrying out of PGD, on the understanding that, in the event this is a couple, the agreement must be signed by both authors of the parental plan (Art. 69). PGD can only be carried out in a fertilisation centre and in a human genetics centre which have drawn up a specific collaboration agreement for this purpose, with the number of fertilisation centres being authorised to practice PGD being limited (Art. 71 and 72).

In the chapter on "*legal conditions*" of PGD, the law prohibits (Art. 67) PGD for eugenic reasons, within the meaning of the Law of 11 May 2003 on research into *in vitro* embryos, i.e. if it is "*based on the selection or amplification of non-pathological genetic characteristics of the human species*"[12], and PGD "*based on sex selection*" within the meaning of the same Law, which provides for an exception for "*selection which enables embryos affected with sex-related diseases to be set aside*" with the idea being that the diagnosis then comprises a therapeutic aim[13]. Given this wording, one must certainly read the law as containing a *general authorisation for PGD, except* when it is of a eugenic nature or based on sex selection, prohibitions to which two exceptions are accepted: the selection which enables embryos affected with sex-related diseases to be set aside and the exceptional authorisation of PGD in a delicate situation which has been the subject of much attention, namely "*in the therapeutic interest of a child already born of the author or authors of the parental plan*",

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[10] *Belgian Official Gazette*, 17 July 2007; commentaries: Derèse M.-N. and Willems G., *R.T.D.F.*, 2008, p. 279; Genicot G., *J.T.*, 2009, p. 17; Nys H. and Wuyts T., *R.W.*, 2007-2008, p. 762. The provisions of the law related to PGD appear to comply with Articles 11 to 14 of the Convention on Human Rights and Biomedicine (opinion of the Council of State of 14 February 2006, *Parl. doc., Senat*e, 2005-2006, no. 3-417/3, no. 152).

[11] Main parliamentary works: bill proposed by Mrs De Roeck, Mrs Defraigne and Mrs Durant and Mr Mahoux and Mr Vankrunkelsven, *Parl. doc., Senat*e, 2004-2005, no. 3-1440/1; opinion of the Council of State of 14 February 2006, *Parl. doc., Senat*e, 2005-2006, no. 3-417/3; report made to the Senate on behalf of the Commission for Social Affairs by Mr Cornil and Mrs De Schamphelaere on 7 June 2006, *Parl. doc., Senat*e, 2005-2006, no. 3-1440/9; report made to the House of Representatives on behalf of the Commission for Public Health by Mr Germeaux and Mr Chevalier on 9 March 2007, *Parl. doc.,* House of Representatives, 2006-2007, no. 51-2567/004.

[12] On eugenics, see the opinion of the Committee no. 33 of 7 November 2005 on somatic and germinal gene modifications for therapeutic and/or meliorative purposes, spec. pp. 10-18 (historic context, definitions, negative eugenics by selection of embryos and/or of the foetus).

[13] On sex selection using PGD, see the opinion of the Committee no. 22 of 19 May 2003 on sex selection for non-medical reasons; Shapira A., "Preimplantation genetic diagnosis and sex selection: should we do it?", in Teboul G. (dir.), *Procréation et droits de l'enfant*, Bruylant/Nemesis, coll. Droit & Justice, 2004, no. 57, p. 49.

provided then that the fertilisation centre consulted considers that "*the parental plan does not have the sole objective of realising this therapeutic interest*" (Art. 68)[14]. It is therefore above all the sensitive question of "saviour children" which has, due to the major ethical implications it comprises, been the subject of parliamentary debates[15], with the exclusion of the one concerned by this opinion.

It is not however without interest to reveal that to the question of knowing if PGD is prohibited when it is in the *therapeutic interest of the child to be born*, particularly with the aim of preventing certain genetic disorders, it was answered that this case "has nothing to do with eugenics and, consequently, does not fall within the remit of the prohibition" and "is hence authorised"[16]. The parliamentary works confirm, incidentally, the reading of the aforementioned text since it emerges from it that *the will of the legislator was not to prohibit, as a general rule, PGD so as to authorise it only in certain exceptional circumstances* – as no one wants - but rather to *leave the management of PGD to procreation and genetics centres and only establish general guidelines* (prohibition of eugenics and sex selection for non-medical reasons)[17]. If one draws a parallel between PGD and *prenatal diagnosis*[18], one will recall that unfavourable PND paves the way for therapeutic abortion, which may be practised after the first twelve weeks of pregnancy and without a maximum period (the viability of the foetus does not constitute an extreme deadline) when it is "*certain that the child to be born* will be *affected with a particularly severe disorder* which is recognised as incurable at the time of the diagnosis" (Art. 350. 2.4 of the Belgian Criminal Code). The central issue is that, if such a disease is considered a severe foetal anomaly authorising therapeutic abortion, the status of healthy carrier will not generally be[19].

The question of *medical indications authorising PGD* is not settled by the law and is therefore part of those which are entrusted to the competent genetics centres, whose excellence of work politicians have agreed to recognise. Hence, the Law of 6 July 2007, which does not have a strictly medical vocation, does not specify (or, more exactly, does not define) the *diseases* which can be considered as sufficiently severe to justify the "setting aside" of one embryo in favour of another. It seems logical to have to deduce from this that, once the diagnosis reveals any kind of "imperfection", a selection may be made, since such is the purpose of this technique. The question of making use of PGD in order to avoid the birth of a

[14] Derèse M.-N. and Willems G., "La loi du 6 juillet 2007 relative à la procréation médicalement assistée et à la destination des embryons surnuméraires et des gamètes", *R.T.D.F.*, 2008, p. 347.
[15] Derèse M.-N. and Willems G., *op. cit.*, pp. 349-350 and the cited refs..
[16] Report made to the Senate on 7 June 2006, *Parl. doc., Senate*, 2005-2006, no. 3-1440/9, pp. 174-175.
[17] Report made to the House of Representatives on 9 March 2007, *Parl. doc., House of Representatives*, 2006-2007, no. 51-2567/004, pp. 46-47. Both in the Senate and in the House of Representatives, amendments were filed in view of authorising only - as is the case in France (Art. L. 2131-4 of the French Public Health Code) - PGD exceptionally, in view of screening a particularly chronic genetic disease recognised as incurable at the time of the diagnosis and which has been specifically identified beforehand in one of the parents and of specifying that PGD can only be performed for finding this disease as well as the means of treating it. These restrictive amendments were rejected.
[18] Nicely presented as aiming to "refuse the worst by elimination", whereas PGD consists of "selecting the best by selection" (Testart J., *La procréation médicalisée*, Flammarion, coll. Dominos, 1993, p. 100). On PGD, we will consult the book by Tilmans-Cabiaux C. and Duchêne J., (eds.), *Risquer de naître. Médecine prénatale et tests génétiques*, P.U. Namur, 2002 and in particular, from a legal standpoint, the articles of Hautenne N. and Tilmans-Cabiaux C.
[19] Cook R.J., Dickens B.M. and Fathalla M.F., "Diagnostics prénatal et génétique préimplantatoire – Risques de transmission de maladies", in *Santé de la reproduction et droits humains. Intégrer la médecine, l'éthique et le droit*, Paris, Masson, 2005, p. 378 (in respect of Ta-Sachs Disease).

child who is a *healthy carrier* of a severe genetic disease has not, *a fortiori*, gained the attention either of politicians or of commentators[20].

To conclude, from a legal standpoint, neither the Belgian Law of 6 July 2007 whose provisions relating to PGD are succinct, nor the parliamentary works which preceded it, expressly prohibit PGD in a situation similar to the one which has given rise to the question presented to the Committee.

3.3. Comparative law / Opinions of ethics committees

The nature and the consequences of preimplantation diagnosis entail in all countries the concern that this practice is strictly supervised. Below we will mention recent relevant documents and analyses.

3.3.1. France

Preimplantation diagnosis has been authorised here since 1994 "exceptionally" when "the couple, due to its family situation, has a high probability of giving birth to a child affected with a particularly severe genetic disease recognised as incurable at the time of the diagnosis"[21]. The practising of this preimplantation diagnosis is subordinate to the prior identification in one of the parents or one of the immediate ancestors - in the case of a very debilitating disease, detected at a late stage and prematurely putting at stake the vital prognosis -, of the anomaly or anomalies responsible for such a disease. Preimplantation diagnosis may only have the purpose of searching for the disease in question and the means of preventing it or treating it. In France, it is mainly used to detect the presence in the embryo of anomalies responsible for very severe disorders, such as mucoviscidosis, Huntington's Disease, haemophilia or certain forms of myopathy, and whose appearance is certain.

In its opinion no. 72 of 4 July 2002 entitled "Reflections on the extension of preimplantation diagnosis"[22], the French National Advisory Committee on Ethics deals with the extension of the use of PGD, but only considers it for the cases of compatibility of HLA* typing with an already sick child (Fanconi's Disease) and in view of avoiding giving birth to a child carrying the Huntington's Disease mutation, when the parent invokes his or her right of not knowing whether or not he or she is personally a carrier of the disease. It is therefore not a question of making use of PGD to avoid the birth of healthy carriers of a seriously debilitating disease, but only "of the extension of PGD no longer purely in the interests of the child to be born but also in the interests of a third party" (parent, brother or sister).

[20] Nys H. and Wuyts T., restrict themselves to stating that PGD aims to select the embryos which are not *infected* with a chronic genetic disorder ("De wet betreffende de medisch begeleide voortplanting en de bestemming van de overtallige embryo's en de gameten", *R.W.*, 2007-2008, p. 775), whereas, according to Derèse M.-N. and Willems G., (*op. cit.*, 347, note p. 251), PGD "is habitually used in order to avoid placing an embryo which would give birth to a child *carrying* a chronic genetic disease" (and who will develop this disease). Nothing can be deduced from this difference in formulation.

[21] The legal system for PGD is mainly defined, in France, by Articles L. 2131-4 and L. 2131-4-1 of the Public Health Code, introduced respectively by the laws no. 94-654 of 29 July 1994 and no. 2004-800 of 6 August 2004.

[22] Available on the website www.ccne-ethique.fr/avis.php?debut=30.

A controversy started to emerge a few months ago around the use of preimplantation diagnosis to search for the *predisposition to some cancerous diseases*. On 12 October 2006, the Biomedicine Agency ordered a report on this subject[23] which concluded that

"Records have shown that a small number of PGD and PND have already been performed in France compliant with the current legislative provisions, for hereditary forms of cancer or within the framework of diseases associated with a risk of cancer. One may expect that the (Centres) are sent more requests in the coming years for this type of indication and that the analysis of the situations to be examined is more difficult. The working group upheld that it was not necessary to modify the current legislative provisions but that it was, however, necessary to direct the (Centres) in their decision by giving them guidelines to attest to the severity and incurable nature of the different cases of hereditary forms of cancers which they will have to examine.

The legal and ethical discussion did not lead the working group to favour PND more than PGD and vice versa. When this choice is possible, i.e. when the couple fulfils the conditions necessary for making use of PGD, it is up to the couple alone to decide, after appropriate information and with the help of appropriate counselling. A survey, carried out within the framework of this reflection, on the requests for information concerning use of PND and PGD suggests that one can expect a progressive increase in requests. This will have to be monitored and anticipated over the long term in order to adapt the means necessary in terms of genetic counselling, MAP (medically assisted procreation) and genetic analyses".

On 28 March 2008, the Biomedicine Agency, noting the conclusions of this report, *approved the extension of use of preimplantation diagnosis to detect the hereditary forms of the most hereditary cancers*. In this context, the French Senate carried out a comparative analysis of the provisions which govern preimplantation diagnosis in the major European countries, particularly in order to know if the rules in force enable the implementation of this technique to *detect the anomalies responsible for certain cancers*[24].

3.3.2. Other European countries

The 29 Recommendations of the European Society of Human Genetics and of the European Society of Human Reproduction and Embryology, have been published under the title "The need for interaction between assisted reproduction technology and genetics"[25].
Here it is recalled that the techniques, both in terms of reproductive medicine and in terms of genetics, are changing rapidly and that they are often applied without actual knowledge of their long-term effects. Both societies therefore stress the need to establish clear protocols on these matters and organise the follow-up, even transgenerational follow-up. They advocate the putting in place of assisted reproduction centres throughout Europe and consider that use of PGD is justified as an alternative to PND when there is a risk of transmitting a hereditary anomaly.

The examination of the foreign provisions does however show that preimplantation diagnosis is still prohibited in Germany, Austria, Italy and Switzerland[26] and that the countries that

[23] Report drawn up upon the request of the Biomedicine Agency and the National Institute of Cancer "Diagnostic prénatal, interruption médicale de grossesse, diagnostic préimplantatoire et formes héréditaires de cancers", available on the website www.agence-biomedecine.fr/fr/experts/pegh-dpi-etudes.aspx.
[24] Comparative legislation report no. 188 of 13 October 2008 on preimplantation diagnosis, available on the website www.senat.fr/noticerap/2008/lc188-notice.html.
[25] "The need for interaction between assisted reproduction technology and genetics: recommendations of the European societies of human genetics and human reproduction embryology", *European journal of human genetics*, 2006, 14, pp. 509-511.

accept it - i.e. Belgium, Denmark, Spain, the Netherlands and the United Kingdom - are extending its scope progressively, but without necessarily planning its use to detect cancerous predispositions. These five countries - which have legalised the use of preimplantation diagnosis, define its legal and statutory scope. It is fitting to note that, in an opinion dated 18 January 2006, the Dutch Gezondheidsraad ruled in favour of the extension of PGD in order to avoid transferring healthy carrier embryos, but provided that this does not imply the use of another cycle of ovarian stimulation[27].

We note that the definition of the anomalies which it is possible to detect using preimplantation diagnosis has barely changed. As a general rule, preimplantation diagnosis is reserved for screening the genetic or chromosomal anomalies responsible for incurable diseases and which appear at an early stage, with the family situation letting it be presumed that a high risk for the embryo existed. So as not to stigmatise those inflicted with diseases, no text provides a list of anomalies which it is legitimate to detect using preimplantation diagnosis. It is the establishments authorised to perform preimplantation diagnoses or the authorities which authorise them to perform these tests which determine the cases in which the use of preimplantation diagnosis is justified.

[26] This prohibition results from the law in Switzerland, Germany and Austria, but not in Italy where the situation could soon change. The Swiss law which governs medically assisted procreation expressly prohibits preimplantation diagnosis. However, the German and Austrian laws include no explicit prohibition, but several of their provisions are incompatible with this practice. In Italy, the law of 19 February 2004 on medically assisted procreation may be interpreted as not preventing the use of preimplantation diagnosis, but the directives taken in July 2004 via regulations for its application exclude unambiguously this practice. As new directives, published in April 2008, have repealed this prohibition, preimplantation diagnosis, which was carried out before the entry in force of the Law of 2004, could shortly be once again offered to couples affected by some genetic diseases.

[27] *Preïmplantatie genetische diagnostiek en screening*, Opinion of the Dutch Gezondheidsraad of 18 January, available on the website www.gr.nl/adviezen.php?Jaar=2006.

4. Ethical considerations

The quality of life of children suffering from a severe hereditary disease can be greatly altered. Even when a disease manifests itself at a later age, it is accompanied generally by major physical and mental pain for the person affected.
Assuring these children of a familial, psychological, medical, social and pedagogic support represents a huge task which requires major personal resources and means. These people furthermore have to benefit from optimum integration in society in respect for their human dignity. It is legitimate for future parents, aware of the fact that they present a risk of giving birth to a severly affected child, take precautions to avoid this. It is also just as legitimate for society to grant these parents the means necessary in this respect.

Insofar as the new technologies - prenatal diagnosis (PND) or preimplantation diagnosis (PGD) - enable it to be determined whether or not a foetus or an embryo is affected, it seems ethically justified to make use of one of these techniques in order to avoid the birth of severly affected children. When the direct detection of an X-linked disease is not possible, the Committee[28] accepts the use of post-conception methods which, alone, offer the necessary guarantees in order to prevent the birth of severely affected children.

4.1. Selecting prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD)

In its opinion no. 18[29], the Committee dealt with in detail the different points of view relating to the status of the embryo and concluded that, within the Committee, two opposing opinions reigned. For some members, from the moment the egg is fertilised, an embryo must be considered a person and therefore be protected and treated as such. These members hence have reticence as to the elimination of healthy carrier embryos. Being, however, mindful of the fact that not all embryos can be transferred, it seems logical to them, when a selection is required, to enable parents to want non-carrier embryos to be selected. Other members are of the opinion that an embryo can only be considered a person as of a certain stage in its development. According to them, an embryo which has just been formed and which is the subject of PGD cannot be assimilated to a person to be protected. They therefore see no moral objection to the elimination of healthy carrier embryos, if such is the wish of the parents.

In the absence of fertility problems, the question may be posed as to knowing whether it is acceptable to proceed with PGD insofar as a prenatal diagnosis is possible. PGD implies, in fact, medically assisted procreation, which is often painful for the future mothers and is accompanied by a certain social cost. *In vitro* fertilisation (IVF) is not without danger, either for the mother (risk of infection, ovarian hyperstimulation syndrome), or for the child (increased neonatal morbidity and mortality).

Furthermore, prenatal diagnosis comprises an increased risk (0.5 in 100) of a miscarriage. If the foetus is affected, this implies an abortion as of three months, which is generally a source of mental suffering for the parents who have already really made an emotional investment in this foetus as becoming their future child. It is, furthermore, possible that several successive pregnancies have to be aborted in order to obtain a non-affected foetus.

[28] Opinion no. 3 of 17 November 1997 of the Belgian Advisory Committee on Bioethics on sex selection.
[29] Opinion no. 18 of 16 September 2002 of the Belgian Advisory Committee on Bioethics on research into the *in vitro* human embryo.

If, for example, the probability of having an affected child is 1 in 4, some couples will have to go through several pregnancies before having a non-affected child.

The members of the Committee who feel that the importance of protecting the embryo increases with the degree of its development could, furthermore, prefer, from an ethical standpoint, the use of PGD, regardless of the complexity, over carrying out prenatal diagnosis. The main advantage of PGD is in fact that it enables an abortion to be avoided; it is revealed that this constitutes the main motivation of most couples who use it, with these couples often having already had the unfortunate experience of an abortion for medical reasons[30].

Remember that in Italy, in 1994 already, 73% of beta-thalassemia patients (an autosomal recessive disorder affecting the haemoglobin) favoured PGD over PND[31].

The members of the Committee feel that it is up to the prospective parents to opt for prenatal diagnosis or PGD if they are likely to give birth to a child infected with a severe disease, even if they are fertile. They recommend that when PND is offered to the families concerned by hereditary anomalies, PGD is also presented as an alternative[32]. They do however agree with the Nederlandse Gezondheidsraad (the Dutch Health Council) when this underscores that "it is fitting to ensure that the possibility of proceeding with PGD does not entail social pressure encouraging its use" and that "the guarantee of solidarity remains a point to which great importance must be given"[33].

4.2. Ethical considerations concerning four different situations

4.2.1. A couple that makes use of assisted reproductive technology (ART) due to fertility problems and that is likely to transmit a mutation causing a severe hereditary disease

If the authors of a parental plan, who present a high risk of giving birth to children affected with a severe disease and wish to avoid it, encounter a fertility problem and have to, in any event, make use of medically assisted procreation, it seems logical that they can use PGD.
They then will ask for embryos affected with the disease not to be transferred. It may be the case that they also express the wish not to have healthy carriers of the disease transferred, in order to spare their descendants the psychological burden of a genetic anomaly and a risky pregnancy.

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[30] Vekemans M., Frydman R. and Munnich A., "Diagnostic pré-implantatoire", *in Diagnostic prénatal, pratiques et enjeux*, Inserm, coll. Questions en santé publique, 2003, p. 54. These authors specify that couples making use of PGD have, in general, already had an infected child and are well aware of the consequences of the disease to be screened. They conclude (p. 57) that "it is fitting to remember at all times that this method of diagnosis was developed solely to respond to the distress of families faced with a child infected with a genetic disease, and this therefore remains its first intention" (translation).

[31] Palomba M.I., Monni G., *et al.*, "Psychological implications and acceptability of preimplantation diagnosis", *Human Reproduction*, 1994, 9, pp. 360-62.

[32] Recommendations of the European Societies of Human Genetics and Human Reproduction and Embryology, "The need for interaction between assisted reproduction technology and genetics", *European Journal of Human Genetics*, 2006, 14, pp. 509-511.

[33] *Preïmplantatie genetische diagnostiek en screening*. Opinion of the Dutch Gezondheidsraad of 18 January 2006, p. 34.

From an ethical standpoint, the same question is posed, since this here is question of eliminating healthy carriers, and therefore children who will not present the disease[34].

All the members of the Committee consider that this request is however admissible in principle and feel that at the time of PGD, the selection of embryos not carrying the mutation may be considered[35].

However, for some members of the Committee, whilst the request is admissible in principle, it is fitting to examine other conditions. Hence, for example, does the elimination of healthy carriers imply the use of a new cycle of ovarian stimulation or not? These members think that if the future parents do not have enough embryos presenting the required development qualities to be able to hope that the pregnancy is successful, there can be no question of accepting their request. According to them, starting a new ovarian stimulation cycle in this case is not justified, given the risks which the woman runs in each stimulation cycle. They feel, furthermore, that the initiation of another ovarian stimulation cycle inappropriately overburdens the ARTcentres and hence represents an unjustified social cost. These members therefore share the opinion of the Nederlandse Gezondheidsraad which recommends limiting the elimination of healthy carrier embryos to situations which do not involve the use of another ovarian stimulation cycle.

Other members consider that it is the future parents alone who have to decide on the risks they are taking and assess whether or not they prefer to start a new cycle, despite the fertility problems which they are encountering. In any event, whether these are parents making use of ART out of necessity, whilst presenting a high risk of bringing a child into the world who is affected with a severe hereditary disease, or whether these are parents who are using it because they want PGD in the absence of any fertility problem (see 4.2.2), it is necessary to consider with them all the possible scenarios, before starting any ART which is accompanied by PGD, and to continue this discussion as each new concrete situation arises[36]. If, for moral or material reasons, the fertility centre itself imposes clear limits, it is essential for the future parents to be informed of this in advance.

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[34] As indicated by Sèle and Testart, "solid safeguards have to be maintained if we want to avoid insensitively going from medically assisted procreation to a veritable genetically controlled pro-eviction". This being so, they admit that once the first objective is achieved, namely "the elimination of embryos presenting the mutation, i.e. those affected with the disease sought", "there are still a number of embryos such that it enables a second or third choice on other criteria. For example, with regards the only identified mutation, one can detect embryos which do not have the disease but are carriers of this mutation. A second choice may lead to eliminating these embryos, not because they have the disease, as they are healthy, but for the unfavourable gene they would be likely to transmit later on" (translation) (Sèle B. and Testart J., "Le diagnostic préimplantatoire: quels outils, pour quelle quête?", in Feuillet-Le Mintier B. (ed.), *Les lois "bioéthique" à l'épreuve des faits. Réalités et perspectives*, PUF, 1999, pp. 161-163). We can reveal that, six years earlier, Testart proposed the banning of PGD (*La procréation médicalisée*, Flammarion, coll. Dominos, 1993, pp. 95-103).

[35] For an in-depth discussion on this point, see Wert G., "Preimplantation genetic diagnosis: the ethics of intermediate cases", *Human Reproduction*, 2005, vol. 20, pp. 3264-3265; to be compared with the reaction of Ray P.F., "Ethics and genetics of carrier embryos", *Human Reproduction*, 2006, vol. 21, pp. 2722-2723. One should also refer to the numerous considerations given by the Committee in its opinion no. 33 on somatic and germinal genetic modifications for therapeutic and/or meliorative purposes.

[36] The Committee subscribes to the aforementioned recommendations made in this sense by the European Societies of Human Genetics and Human Reproduction and Embryology (*European Journal of Human Genetics*, 2006, 14, pp. 509-511) as to the pressing need for correct diagnosis and complete genetic, medical and psychological counselling, both before and after PGD. These recommendations include the fact that only considering PGD in the context of all the other possible options, by carefully assessing its advantages and disadvantages, and only performing it if the couple agrees to know the result and accepts all its implications.

4.2.2. A couple without fertility problems makes use of PGD to avoid giving birth to children suffering from a severe hereditary disease

The situation may arise when the woman is a carrier of a mutation on an X chromosome. Even though the parents have opted for PGD in order to select non-affected embryos, on this occasion, it might be the case that they also refuse the transfer of healthy carrier embryos[37].
As in the cases described above, this request is admissible in principle and, at the time of PGD, the selection of embryos not carrying the mutation may be considered.

However, still as in the situation in 4.2.1., some members feel that the response to this request depends on the number of quality embryos which the couple has. For these members, the morphological quality of the embryos may be a preponderant element in the decision to transfer or potentially to start another cycle of ovarian stimulation.

Other members consider that it is the parents alone who should chose to initiate a new ovarian stimulation cycle if only the healthy carrier embryos are quality ones. For these members, this situation is absolutely not the same as that of parents faced with fertility problems. In the cases being looked at here, it is in order to avoid giving birth to children infected with a severe disease that parents use ART, which is not in itself harmless, particularly for the woman. If the mother decides that she prefers to undergo another cycle in order to avoid the birth of a healthy carrier child who is likely to transmit the mutation to the next generations, particularly to one of the child's daughters who will, herself, have to make use of ART, where appropriate, these members consider that this question is justified.

4.2.3. A couple without fertility problems wishes to make use of PGD solely to avoid giving birth to healthy carriers of an X-linked disease

The question of the merits of eliminating healthy carrier embryos is posed differently here. In this case, the purpose of using PGD is not to avoid giving birth to affected children, but solely aims to avoid giving birth to healthy carrier children.

When the father is a carrier of an X-linked disorder, all the children will be healthy, but the daughters will be carriers of the disorder. The healthy carrier daughter risks giving birth to an affected son and the parents fear that the father's disease will be present in one of their grandchildren and, in the worst case, will give rise to new tragedies in the next generations. Some people have suffered from the existence of a hereditary disorder, particularly to find a partner, and want at any cost to avoid the reproduction of this disorder in the future generations. We can indeed easily understand that parents with good intentions for their children wish to protect them against future problems. When the father affected with the X-linked disorder has suffered greatly from his handicap, it seems quite understandable that he in no way wishes for one of his grandsons to suffer as a result of this.
As specified by the Nederlandse Gezondheidsraad, it is impossible to give an objective scientific definition of a "severe disease", since it depends in particular on what has been experienced by the family. From a purely psychological standpoint, for the personal balance

[37] In this respect "to ignore the information regarding carrier status seems to be problematic, whereas the pre-selection of non-carrier embryos is obviously reasonable, as this may avoid the occurrence of difficult reproductive decisions for future women"; "the additional selection against female carrier embryos may well be morally justified" and "the loss of healthy female embryos would not be disproportionate" in view of "avoiding reproductive dilemmas for future children related to serious health risks for the grandchildren", such that "the health benefit is transgenerational" (de Wert G., "Preimplantation genetic diagnosis: the ethics of intermediate cases", *Human Reproduction*, 2005, vol. 20, pp. 3264-3265).

of the father, we understand his concern for avoiding carrying the guilt of having transmitted a debilitating gene to his descendants.
If their daughter, a healthy carrier of the X-linked mutated gene, wishes to avoid giving birth to an affected son, she may potentially opt for PGD to detect the mutation. Concomitantly, she may decide to avoid the birth of a healthy carrier daughter. This situation is similar to the one described in point 4.2.2..

However, won't the evolution of technology enable the easier avoidance of the birth of children affected with a chronic disease in 20 years' time and won't the complexity of ART significantly reduce in the not so distant future? In the end, the prospective parents state their wish that the problems are resolved today radically which tomorrow will not perhaps be posed.

The questions, which this situation raises, evoke the right of parents to decide on living conditions which they deem acceptable for a child. Faced with the dilemmas which this may entail, some members of the Committee consider that it is clearly up to the parents to decide what they feel to be the most ethical: to prevent at all costs potential later complications for their descendants and, where appropriate, undergoing another cycle of ovarian stimulation, or to hope that their children are spared of it or will have the strength and the means to cope with it.

Other members feel that in principle access must never be given to a request for PGD when this solely is to avoid the transfer of healthy carrier embryos, since these children are healthy. Whilst they clearly understand the concern of parents who wish to avoid unpleasantness for their future children, they do however find that they must hear reason, given the current cost of ART and PGD for society and more specifically for the medical teams. Nothing, in their eyes, justifies such investments being made today when this is a case of protecting future generations for which the problem may perhaps never arise for example if the descendant does not wish to procreate, and, if this arises, has great opportunities to resolve this more easily. They feel that this parental request is disproportionate. Whilst they concede that it is normal for future parents to want the best for their children, they note that any life is a risky undertaking and that it is impossible, or even harmful, to want to protect these children against all the future misfortunes which may occur to them.
Among these members, some adopt a more clear-cut position and contend that it is justified, from an ethical standpoint, to take account of the experience of the applicant parents. In exceptional situations, they feel it admissible, mainly for psychological reasons, to take their request into consideration. Indeed, once adults, these children themselves become prospective parents who may be faced with the same difficulties as their own parents. At first sight, it seems understandable that the latter wish, as far as possible, to spare them this burden. Some parents may also fear the reaction of their children when they have to explain to them that they are carriers of a mutation. One might conceive that these healthy carriers can reproach their parents for having placed satisfying their desire to have children before the quality of life of their children. Other parents fear that their children, when the moment comes, will not perhaps take account of the hereditary risk. They consider that it is their own responsibility to do everything possible for this familial disease to disappear.

Other members still feel that it is impossible to shelter children from all risks of life. They feel this situation is however particular, insofar as this is not a question of protecting the child against an indefinite risk which he or she may potentially run but of sheltering it from a certain risk, particularly of having to make difficult reproduction-related decisions, that by default one makes him or her run in knowledge of the facts.

These members also remark that it is not only impossible to predict the future of these children and therefore anticipate their own potential desire to have children, but also to predict their attitude faced with the risk they present in giving birth to children affected with a severe hereditary disease. Whilst all members agree on saying that it is essential, when a child is or could be a healthy carrier of the mutation causing a severe hereditary disorder, that this problem is the subject of an open discussion within the family, some members remark that the fact of "knowing" everything about the clinical expression of a severe hereditary disease does not imply necessarily the ability to assume it. Faced with an embarrassing reality, some people go into denial. When the prospective parents doubt the ability their children will have to manage responsibly the fact of being a healthy carrier of a mutation causing a hereditary disorder, this doubt justifies, ethically, their request to avoid the transfer of healthy carrier embryos. Insofar as the mutation can be transmitted to several generations, they feel it imprudent to transmit it consciously.
For these members, it is above all up to the parents to decide whether or not they accept confronting their children with this type of problem. These members are far from insensitive to the question of the overload which use of PGD would impose on the genetics and ART centres, even on the prospective parents who might not be treated in the desired time, but they feel it is up to society to provide the centres with the means necessary for this purpose. Nothing, incidentally, enables it to be excluded that society does not benefit from this, in the longer term.

4.2.4. A couple without fertility problems wishes to make use of PGD solely to avoid giving birth to healthy carriers of an autosomal recessive disorder

Here we will discuss in detail two relatively frequent diseases: mucoviscidosis and sickle-cell anaemia. For mucoviscidosis, the situation is only problematic when both parents are carriers. There is a 1 in 4 risk that the child is affected. Two embryos will be healthy carriers of the gene and one will neither be affected nor a carrier. As the disease is highly debilitating, it is ethically justified to determine whether or not we are dealing with an affected embryo. In case of PGD, the problem of eliminating healthy carrier embryos can be posed. The risk that a carrier of a recessive gene meets another carrier is however relatively low (1 in 20), such that it seems less legitimate to set them aside for this reason alone.

In the case of sickle-cell anaemia, an anomaly of the haemoglobin which is also very painful for the affected person, the ethical problem is more complex. The incidence of healthy carriers of sickle-cell anaemia in regions rife with malaria, particularly when *Plasmodium falciparum* is the infectious agent, is constantly increasing. Carriers of sickle-cell anaemia benefit, in fact, from natural protection against the often fatal neurological complications of malaria. Their number is increasing therefore within the global population, such that the risk that both parents are healthy carriers of the mutation causing the anaemia is increasing, just as, consequently, is the number of sick children.

We could therefore advocate an elimination of carrier embryos in order to reduce the number of patients suffering from sickle-cell anaemia. However, given that there is still no effective treatment against cerebral malaria, this scenario implies an increase in the number of deaths caused by malaria, at least in black Africa, in some regions of Asia and in South America. But the incidence of sickle-cell anaemia is also increasing in the rich countries (1 in 2,000 births), where malaria is absent. Here, therefore, the question is clearly posed of the potential ethical justification for eliminating healthy carrier embryos. This will, nevertheless from a statistical point of view, have very little if any effect on the incidence of anaemia.

For their own reasons, some parents, one of whom is a carrier of an autosomal recessive disorder, may have developed excessive anxiety as to the idea of transmitting this mutation to their children. This may be the case for mucoviscidosis, since the carrier parent may have lived with affected people in his or her close family. As has been previously indicated, the risk of meeting a partner who is also a healthy carrier of the anomaly is currently 1/20. Given the complexity and the cost of PGD, it seems barely legitimate, from an ethical standpoint, to allow the request for PGD which would be formulated by the prospective parents when only one parent is a carrier of the mutation and when there is therefore no risk of giving birth to an affected child[38]. Some members do however think that if, after multiple interviews with *ad hoc* specialists, the future parents do not succeed in putting their fear into perspective and will therefore not go ahead with a desire for a genetically parented child through fear of giving birth to a healthy carrier child, their request needs to be examined favourably, and potentially access to it should be granted exceptionally.

5. Conclusions and recommendations

This opinion concerns the use of PGD to detect embryos which are *healthy carriers* of a mutation causing a severe hereditary disease for which offspring can have an increased risk.

The use of PGD for this purpose must be distinguished from when it is used to prevent the birth of a child *affected* with the disease.
When parents have a high risk of giving birth to a child affected with a severe hereditary disorder, all members of the Committee feel that it is up to the parents to decide, after specific genetic counselling and information, on what technique they wish to use, if they wish to avoid the risk of giving birth to a child affected with a severe disease. In other words, in this hypothesis, the use of PGD should be possible, even in the absence of any fertility problem.

When PGD is used to detect healthy carrier embryos, different situations may be distinguished:

a. *The couple has fertility problems and risks transmitting a mutation causing a severe hereditary disorder (i.e. high risk of an affected child).*

If the couple uses PGD to avoid the birth of an affected child and concomitantly asks for healthy carrier embryos not to be transferred, all the members of the Committee consider that this request may be admissible.

Some members consider that such a request can only be contemplated provided that it does not require a new cycle of ovarian stimulation. According to these members, the choice of embryos which will be transferred depends, first of all, on their morphological quality. In the event several embryos with a satisfactory morphological quality are available for transfer, non-carrier embryos will be transferred preferably.

For other members, it is the request of the parents which takes precedence and it is up to them in particular to decide whether or not they want to take the risk of starting a new cycle of ovarian stimulation in order to avoid transferring healthy carrier embryos. These members

[38] On this point, see Wert G., "Preimplantation genetic diagnosis: the ethics of intermediate cases", *Human Reproduction*, 2005, vol. 20, p. 3264 : "in view of the (very) low risk that the future carrier will be faced with difficult reproductive decisions, it would be disproportional to categorically discard these (healthy) embryos, and to start a new IVF/PGD treatment. I assume that prospective parents will agree, at least after adequate counselling".

consider, nevertheless, that it is society's responsibility, where appropriate, to make the necessary means available to the ART centres and genetics centres so that accepting such requests does not delay the treatment of other patients.

b. When *the couple does not have fertility problems, uses PGD to avoid giving birth to children affected with a chronic hereditary disease* and concomitantly does not want the healthy-carrier embryos of this disease to be transferred, the positions of the members of the Committee are the same as those given for the situation above.

c. In the situation where *the couple with no fertility problems wishes to use PGD solely to avoid giving birth to healthy carriers of an X-linked disease,* the use of PGD seems more questionable.

Hence, some members of the Committee feel that in principle access must never be given to a request for PGD when this *solely* is to avoid the transfer of healthy carrier embryos, since these children are healthy. Making use of complex technologies is not acceptable in their eyes, especially given that it is impossible to predict if these future adults will develop a desire to have children and that, furthermore, it is likely that, in 20 years' time, we will have less complex and cheaper technological means of avoiding the birth of a severly affected child. They think that such a request testifies to the existence of a disproportionate need to protect ones children against all risks of life.

According to other members, the request for PGD solely in view of avoiding giving birth to healthy carriers is admissible, but only on a completely exceptional basis. They consider this request excessive, given the complexity of PGD, the cost for the centres which treat it and the risks incurred by the woman. Some parents may nevertheless have developed such an apprehension in respect of a hereditary disease from which they themselves have suffered, that it is impossible for them to satisfy a desire to have children when they are not certain of not passing on the mutation to their descendants. In these exceptional cases, these members consider that it may be legitimate to make an exception to the general rule which consists of refusing PGD in this case, and therefore accepting their request.

Finally, other members think that, in terms of trying to ensure their descendants avoid living identified and foreseeable difficulties, it is acceptable, from an ethical standpoint, to leave it up to the parents to decide. PGD to avoid giving birth to healthy carrier children must, in their opinion, be accessible to them if such is their wish.

d. *The couple without fertility problems wishes to make use of PGD solely to avoid giving birth to healthy carriers of an autosomal recessive disorder.*
Accepting the request for PGD solely to avoid giving birth to healthy carriers of an autosomal recessive disorder seems more problematic still, given the fact that the risk which this child meets, later on, a partner who is also a healthy carrier of this mutation is relatively low. According to all members of the Committee, these requests should in principle be refused. Some members nevertheless think that, in rare cases, the experience of a parent in relation to this anomaly may be so bad that they will abstain from any procreation if they are not certain that "their pathological gene" will no longer be transmitted. These members therefore advise examining these situations on a case by case basis and, if necessary, exceptionally granting access to PGD, despite its complexity and its cost.

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Glossary

- **autosomal dominant disease**: "A disease which is manifested further to a mutation of one of the two alleles of a pair of autosomes is called autosomal dominant. There is a one in two chance that a child of whom one of the parents is affected with an autosomal dominant disease is affected with the same disease." An autosome is any chromosome other than the sex chromosomes - in the human being, these are chromosomes 1 to 22. (Evers-Kiebooms G. et Welkenhuysen M. (eds), *Die ziekte in mijn familie, krijg ik die later ook?: predictieve genetische tests*, Leuven, LannooCampus, 2005, p.315, translation).
- **autosomal recessive disease**: "Monogenic diseases are hereditary diseases caused by the deficiency of a single gene of the DNA of the nucleus of a cell. As all genes are inherited in two copies (two "alleles"), one coming from the father and the other from the mother, it is fitting to make a distinction between the "dominant*" diseases and the "recessive" diseases. For the first to appear, only one of the two alleles has to be abnormal: the appearance of the second, however, requires that two alleles are abnormal. A recessive disease requires the presence of the anomaly on both genes, one inherited from the father and the other from the mother." (Serres M. and Farouki N., *Le livre de la médecine*, Poitiers, Le Pommier, 2001, pp. 396-397, translation).
- **X-linked disease**: "Of the monogenic diseases, those which are caused by the deficiency of a gene carried by a sex chromosome (X chromosome) are particular and are called "sex-linked diseases". The other diseases, caused by a gene carried by a non-sex chromosome are called "autosomal diseases". Diseases linked to the Y-chromosome have still not been identified. This means that sex-linked diseases are due to deficiencies of genes carried by the X chromosome. They are in general recessive, i.e. that the presence of a normal allele removes the abnormal trait." (Serres M. and Farouki N., *Le livre de la médecine*, Poitiers, Le Pommier, 2001, p. 397, translation).
- **embryo biopsy**: the taking of a sample of one or several cells from an embryo with 6 to 8 cells.
- **expression of a mutation**: "The way in which a mutation or the genotype is manifested at the phenotype level, for example by more or less pronounced pathological symptoms" (Evers-Kiebooms G. and Welkenhuysen M. (eds), *Die ziekte in mijn familie, krijg ik die later ook?: predictieve genetische tests*, Leuven, LannooCampus, 2005, p.316, translation).
- **FISH or Fluorescent In Situ Hybridisation**: the FISH technique is a molecular genetics technique which "consists of locating, using a fluorescent probe, a specific area of the genome, either a mutated area or a chromosome. (...) It is used to detect chromosome anomalies (for example, numeric or structural anomalies) and to determine the sex." (Englert Y., "Fluorescent in situ hybridisation (FISH)" in Hottois G. and Missa J.-N. (eds), *Nouvelle encyclopédie de bioéthique*, Brussels, De Boeck University, 2001, p. 468, translation)
- **polar body**: "In some cases (maternal-origin genetic disease), one can analyse the egg directly by examining the first and potentially the second polar body expelled as the egg is being formed: if the abnormal gene is found in one of the polar bodies, it is therefore not in the egg. This here is pre-conception diagnosis (only the healthy eggs are fertilised) which can only be used for maternal-origin diseases and can cause additional problems of reliability for some specific indications." (Englert Y., "Diagnostic préimplantatoire (DPI)" in Hottois G. and Missa J.-N. (eds), *Nouvelle encyclopédie de bioéthique*, Brussels, De Boeck University, 2001, p.276, translation).
- **HLA or Human Leukocyte Antigen**: "Human leukocyte antigens involved in the acceptance or rejection of grafts or tissue and organ transplants. These antigens are

present on the surface of most somatic cells, with the exception of erythrocytes, but are easier to study on leukocytes" (King R.C. and Stansfield W.D., *A dictionary of genethics,* Oxford university press, 2002, sixth edition, p. 185,).

- **PCR or Polymerase Chain Reaction**: the PCR technique is a molecular genetics technique which "consists of coupling the DNA into fragments and then amplifying a segment to be studied by recopying the sequence a great many times in order to make it legible. (It) enables a fragment of DNA to be read accurately and is used to identify the mutations of a single gene: the typical example of a monogenic disease is mucoviscidosis." (Englert Y., "Polymerase chain reaction (PCR)" in Hottois, G. and Missa, J.-N. (eds), *Nouvelle encyclopédie de bioéthique*, Brussels, De Boeck University, 2001, p.650, translation).
- **Fragile X Syndrome**: "Moderate degree of mental impairment (IQ of around 50) present in male subjects carrying an X chromosome with a fragile site (...). Its frequency (...) is about 1.8 in 1,000. The mental impairment linked to the X chromosome is responsible for approximately 25% of all mental impairments observed in male subjects. The fragile X chromosome contains a gene which is expressed in human brain cells." (King R.C. and Stansfield W.D., *A dictionary of genethics,* Oxford university press, 2002, sixth edition, p. 148,).

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The working documents of select commission 2008/1 – request of opinion, personal contributions of the members, minutes of meetings, documents consulted - are stored as Annexes 2008/1 at the Committee's documentation centre, where they may be consulted and copied.