Organisation des Nations Unies pour l'éducation, la science et la culture
United Nations Educational, Scientific and Cultural Organisation

Comité international de bioéthique (CIB)

International Bioethics Committee (IBC)

Distribution: limited

SHS-EST/02/CIB-9/2 (Rev. 3)
Paris, 24 April 2003
Original: English

Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention

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(SHS-2003/WS/26)

I. INTRODUCTION

1. The Universal Declaration on the Human Genome and Human Rights, in Article 2 concerning its implementation, underscores the need to identify practices such as germ-line interventions that might be contrary to human dignity and assigns responsibility for this to the International Bioethics Committee of UNESCO (IBC).

2. Moreover, in the recommendations adopted at its Second Session (Paris 12-14 May 2001), the Intergovernmental Bioethics Committee (IGBC) "invites the IBC when outlining its detailed two year work programme, to consider at its earliest convenience the inclusion of the following topics: (i) Pre-implantation genetic diagnosis, (ii) Interventions on germ-line cells".

3. At its Eighth Session (Paris, 12-14 September 2001), the IBC therefore retained these two topics in its work programme for 2002-2003 and set up a Working Group chaired by Prof. György Kosztolányi (Hungary) that met for the first time at UNESCO Headquarters from 23 to 24 April 2002 in the presence of Prof. André van Steirteghem (Belgium), an international expert on assisted reproductive technology (Annex I, Composition of the Working Group). The IBC considered a draft report during its Ninth Session (Montreal, 26-28 November 2002), after which the Working Group met for a second time to finalize the report (Monaco, 3 March 2003).

4. It should be recalled that certain previous reports prepared within the framework of the deliberations of the IBC are particularly relevant to the subjects under consideration. These include the "Report on Genetic Screening and Testing" (1994), the "Report on Genetic Counselling" (1995) and the "Report on Human Gene Therapy" (1994).

II. CONTEXT

5. During recent decades fundamental research in genetics has developed at an increasing pace. In human genetics new insights into the molecular background of diseases and new technologies, especially of DNA analysis, have enabled the early and exact diagnosis of an increasing number of congenital disorders, the identification of parents at increased risk of having affected offspring and genetic counselling.

6. In most wealthy countries a new medical discipline, clinical genetics, has been incorporated into specialized medical care. Most clinical genetics centres provide services for the laboratory diagnosis of chromosomal abnormalities and single gene disorders and genetic counselling. Since the late sixties collaborative efforts between departments of obstetrics and gynaecology and clinical genetics have resulted in facilities for prenatal diagnosis. Pregnant women at increased risk of having a child with a genetically-caused disease or malformation may undergo chorion villus sampling (around the 11th week of pregnancy) or amniocentesis (at 16 weeks) and, after cultivation of foetal cells, chromosomal, biochemical or DNA analysis may reveal whether the unborn child is affected by one of the specifically tested abnormalities. If this is the case the prospective parents are confronted with the decision of whether to terminate the pregnancy, thereby avoiding the birth of an otherwise severely affected child.

7. An alternative, non-invasive method of prenatal diagnosis is ultrasound examination, which reveals major structural and sometimes functional foetal abnormalities usually later in pregnancy. Experimental work is being done regarding the diagnostic analysis of foetal cells in maternal blood.

8. There is professional agreement about the major indications for prenatal diagnosis. Most women in developed countries are aware of the possibility of prenatal diagnosis and, in many countries, the costs are covered by public means c.q. health insurers. However, in developing countries, prenatal diagnosis is accessible only to a limited part of the population or it is not available at all. In several developing countries information may not be readily available or the procedure is not accepted.

9. Pre-implantation genetic diagnosis (PGD) can be considered a new approach towards early diagnosis of genetic disease. It became possible only after the clinical establishment of in vitro fertilisation (IVF) (in 1978 in the United Kingdom) for infertile couples and the development of sufficiently sensitive techniques to analyse chromosomes or genes at a single-cell level.

10. The technique is based on IVF; cell division in most cases up to 8-cell stage embryos, biopsy of 1 or 2 cells, analysis by DNA technology for specific genetic abnormalities and selection of unaffected embryos for transfer to the uterus.

11. The first PGDs were published around 1990. Since then a few dozen centres have acquired the highly specialized, multidisciplinary expertise required for the technique. In Europe and North America several thousand PGDs have been established and several hundred (healthy) babies have been born as a result. PGDs have so far been performed for major chromosomal aberrations and some 30 different monogenic diseases. It is likely that in the near future the scope of PGD will be widened to many other conditions, including major multifactorial diseases in adulthood.

12. During the last years it has become more and more customary to test 6-8 cell embryos collected for IVF in infertile couples for chromosomal abnormalities and to transfer only 1-2 embryos found to have a normal number of chromosomes. The expectation is that this selective transfer will result in a higher pregnancy rate and a lower risk of spontaneous abortion.

13. Several centres also accept sex selection under certain conditions. Most recently there have been a few examples of selecting embryos with certain immunogenetic characteristics to function after birth as blood stem cell donors in order to save a sibling with a genetic blood disease or leukaemia that is fatal without compatible hemopoietic stem cell transplantation.

14. These last three examples of PGD application do not aim to avoid severe congenital disorders. Instead the purposes are technical (to improve the results of IVF) or the selection for a desired characteristic (such as male or female sex) or for use in subsequent donorship.

15. The purpose of this report is to describe PGD and discuss the major ethical issues related to its applications and to review the ethical aspects of germ cell intervention in this context.

III. PREIMPLANTATION DIAGNOSIS (sensu stricto)

1. Methodology

16. PGD is based on the IVF procedure originally intended and still most often used for infertile couples. This procedure involves hormone treatment to hyperstimulate the ovaries and the invasive procedure of oocyte retrieval. Treatment occurs over 1-8 cycles, with an average of 12 oocytes retrieved per cycle. The hormone treatment involves some medical risk (1%). After the oocytes are retrieved, they are fertilized using the husband's sperm, with about a 70% success rate. In case of male infertility or as a means of avoiding contamination of the subsequent laboratory analysis, intracytoplasmic sperm injection (ICSI) may be used.

17. About 70% of the fertilised eggs will develop under in vitro conditions to the 8-cell stage embryo at day 3. Using micromanipulation, 1-2 cells are biopsied from the 8-cell embryo and analysed in a highly specialized laboratory. About 80% of the blastomeres are suitable for biopsy and a diagnostic result will be obtained in 90-95% of the biopsied blastomeres.

18. Depending on the indication specific tests are performed to detect abnormalities at the gene or chromosome level. The most common methods are fluorescence in situ hybridisation (FISH) to detect chromosome abnormalities and a variety of DNA analyses using the polymerase chain reaction (PCR) to detect specific single gene mutations known to be associated with severe genetic disease. There is limited experience in testing for about 30 different monogenic diseases and about 1% are misdiagnosed, as revealed by follow-up studies.

19. Biopsied embryos found to be affected are discarded or frozen for research and 1-2 non affected embryos are transferred to the uterus on day 5. Some centres may transfer more than 2 embryos thereby further increasing the rate of multiple pregnancies with the accompanying problems of foetal loss, premature birth and related complications. Even after transferring 2 embryos, the average rate of twin pregnancy is 25%.

20. After embryo transfer the pregnancy rate is 15-25%; centres with great expertise report a pregnancy rate of 40% after 2 or more cycles. At day 10-14 a hormone test is performed to verify if the transferred embryo(s) has implanted and at 7 weeks ultrasonic control of the foetal heart action is carried out. Since PGD is still considered an experimental procedure, it is recommended that the early diagnosis is followed-up with “conventional” prenatal testing using analysis of chorionic villi or cultured amniotic fluid cells.

21. An alternative procedure is the genetic analysis of the polar body of a single oocyte, which has the ethical advantage that no embryo is involved. However, the diagnostic disadvantage that only maternally inherited problems can be detected.

22. Genetic analysis has been attempted at a later stage of embryo development (i.e. the blastocyst stage of about 100 cells reached at day 5-7). The advantage is that more (5-12) extra-embryonic cells from the so-called trophectoderm can be removed and analysed. A major drawback is that very few embryos reach this stage under in vitro conditions. So far no PGD has been clinically performed after 5-6 days of culture.

23. Some follow-up studies of babies born after PGD have revealed an increased incidence of congenital malformations or genetic diseases as so-called imprinting disorders. Other studies did not indicate an increased risk that could be specifically attributed to IVF/PGD. Clearly more well controlled follow-up studies must be performed before a definite answer can be given. However, IVF as a prerequisite for PGD is associated with some risks for the future child especially the high proportion of multiple pregnancies that may result in premature births and the associated complications.

24. For each new indication, the PGD procedure has to be tested experimentally and, as a result, couples at risk for a specific rare genetic disease, often must wait 6-12 months before a PGD can be attempted at the clinical diagnostic level.

2. Indications

25. The three main categories of couples who are referred for PGD are:

- couples at high risk of having a child affected by a genetically-caused disease or malformation, and who have an infertility problem;

- couples at high genetic risk who have undergone "conventional" prenatal diagnosis and who did terminate recurrent pregnancies after an affected foetus was found;
- couples at risk of giving birth to a child affected by a genetically-caused disease or malformation and who object to termination of pregnancy.

26. In addition, older couples referred for IVF because of infertility may request PGD of chromosomal abnormalities (see Section 5a).

27. One group at increased risk of affected offspring includes carriers of a balanced chromosome translocation. In this situation the risk of offspring affected by an unbalanced chromosomal abnormality may be very high.

28. In some instances the risk of a numerical chromosomal abnormality due to the advanced age of the mother is a reason for PGD.

29. A third high-risk group includes those couples where carriership of a single-gene mutation is involved. In case of autosomal recessive conditions such as hemoglobinopathies, cystic fibrosis or spinal muscular atrophy, both partners carry a recessive mutation and are not clinically themselves affected by the disease. Their probability of conceiving and giving birth to a child who inherits the mutation from both parents and who will be affected by the disease is 25%. When the mother is a carrier of an X-linked mutation, such as the ones that cause Duchenne muscular dystrophy, X-linked mental retardation and haemophilia, each son will have a 50% chance of inheriting the disease. In the case of a dominant gene mutation, such as with myotonic dystrophy or the late onset Huntington's disease, a mutation in one of the chromosomes is sufficient to develop a disease; here the risk of couples to give birth to an affected child is 50%.

30. Of the more than 1,000 PGDs reported so far an equal number of referrals were made due to an increased risk of chromosomal abnormality and those due to risk of a monogenic disease.

31. However, during the last year, the relative number of chromosome analyses related to the normal IVF procedure has increased. In future years, the scope of indications for PGD of monogenic diseases is likely to widen because a total of more than 5,000 rare diseases are known to be associated with a single-gene mutation; most of these will be identified in the coming years. Since the technology of DNA mutation analysis is continuously improving it is likely that, in the long term, all monogenic diseases will be diagnosable both by conventional prenatal diagnosis and by PGD.

3. Organisation and Regulation

32. PGD requires a multidisciplinary approach. Usually referral to a fertility clinic takes place after genetic counselling in a clinical genetics centre. In the case where one of the parents, one or more children or close relatives are affected, an accurate clinical and laboratory diagnosis must be performed to enable proper genetic counselling and to establish an indication for PGD. After referral to the fertility clinic a proper evaluation of the clinical aspects of hormone treatment, oocyte retrieval and IVF must be carried out. The counselees must be informed about these clinical aspects and about the possibilities and limitations of the IVF and PGD procedures. The 8-cell embryo selection procedure must be thoroughly discussed as must the fate of supernumerary unaffected embryos or those carrying genetic or chromosomal abnormalities. Information is especially important about the relatively low birth rate after IVF and PGD and, of course, the risk and disadvantages of a multiple pregnancy.

33. Chromosome or gene mutation analysis of 1-2 blastomeres is usually performed in a highly-specialized laboratory associated with both the department of clinical genetics and the fertility clinic.

34. The complexity of the multidisciplinary approach has so far limited the application of PGD. The European Society of Human Reproduction and Embryology (ESHRE) formed a PGD Consortium in 1997 with the aim of undertaking a long-term study of the efficacy and clinical outcome of PGD. The third report of the ESHRE PGD consortium (May 2001) involved 25 centres and reported on 1560 referrals during the past three years. Recently, the number of participating centres has increased to 32.

35. About one quarter of the couples applying for PGD have one or more children affected by a genetically-caused disease or malformation and an even larger percentage have experienced spontaneous abortions or termination of pregnancy after "conventional" prenatal diagnosis. The ESHRE also reports an increasing number of chromosomal analyses associated with normal IVF. Three centres submitted data about sex selection for social reasons. The existence of the PGD Consortium enabled a survey about the acceptability of non-medical reasons for PGD and 15 of the 21 centres that replied were against it.

36. For a multidisciplinary approach to PGD close collaboration between the various units and professionals is to be preferred. In about half the cases the various experts work at the same location but in other instances, especially in the United States, a fertility clinic may be more than 1300 kilometres from the laboratory where the diagnostic analysis is performed. As a consequence blastomeres have to be transported over a long distance.

37. Another problem is quality control. This applies to the clinical and laboratory methods, to the indications for PGD used and to the counselling procedures and efficacy.

38. In most European centres PGD is regulated within the context of IVF in fertility clinics and genetic counselling and often laboratory diagnosis in clinical genetics centres. Professional organizations have defined recommendations concerning indications and quality control. For instance, in France, Spain, Sweden and the United Kingdom, PGD legislation has been implemented. In Belgium, Israel, The Netherlands, Italy and Greece, PGD is allowed under guidance of a national authority; usually PGD is allowed for all diseases amenable by "conventional" prenatal diagnosis. In Europe, public funding is often available via insurers or national/regional governments. For the clinical use of PGD, consent of local ethics committees is required. In some instances a national authority has to review the case.

39. In the United Kingdom, the Human Fertilisation and Embryology Authority has to grant permission for each new disorder to be tested. At the European level, the Council of Europe Convention on Human Rights and Biomedicine (1997) states in Article 36 that countries which already had legislation permitting more about PGD than the Convention does may opt out. Key clauses regarding PGD (Art. 18) read:

- Where the law allows research on embryos in vitro it shall ensure adequate protection of the embryo;
- The creation of human embryos for research purposes is prohibited.

40. In various countries such as Austria, Germany, Ireland and Switzerland, PGD is not allowed; in Australia some states e.g. Western Australia have prohibited PGD while others, South Australia and Victoria, permit its use.

41. In the United States of America, the situation seems even more complex. Not only are there differences among states, the main centres performing PGD are private institutions. At the federal level there has been a ban on public funding of research on embryonic cells and private institutions have a considerable freedom in deciding about the indications and

methodologies of PGD. Since 85% of the costs of IVF are not covered by insurance, individual couples seeking PGD are confronted with high costs. In different publications the estimates for the cost of PGD vary from $15,000 to more than $100,000 depending also on the number of cycles involved. Consequently, in the United States of America, PGD seems to be accessible only to at-risk couples who are in a financially strong position

4. Comparison between PGD and "conventional" prenatal diagnosis (PD)

42. Most experts consider PGD as an additional option for couples at increased genetic risk of giving birth to a child with a genetically-caused disease or malformation and not as a replacement for "conventional" prenatal diagnosis (PD) by amniocentesis or chorion villus biopsy.

43. A major technical difference is that PGD is still considered to be a highly specialized experimental procedure with a limited scope; only a few hundred healthy children have been born during the past decade as a result of PGD. PD has a 30 year history of clinical application. Annually hundreds of thousands couples undergo amniotic fluid (cell) or chorionic villus analyses. A full chromosome pattern and about 1,500, usually rare, monogenic diseases can be tested, whereas in PGD only a limited number of chromosomal abnormalities and some 30 monogenic diseases can currently be tested in 1-2 embryonic cells. Amniocentesis may include biochemical testing for open neural tube defects; this is not possible in PGD or chorionic villus sampling.

44. Another major difference between PGD and PD is cost and accessibility. PD costs between $580 and several thousand dollars. In most developed countries this will be covered by health insurers as clinical genetics services including PD are incorporated into the health care system. As mentioned above, the cost of PGD varies considerably in different centres and states and also according to the number of cycles and the type of analysis. However, in all instances, the cost is between about $40,000 and $100,000. In many instances, especially in the United States of America, couples have to pay themselves.

45. PGD and PD are similar in that they offer couples at increased risk an opportunity to give birth to a child without a genetically-caused disease or malformation. In PD, this approach may be at the cost of terminating a pregnancy at 11-19 weeks. In PGD, abortion is avoided, but parents are confronted with the selection of genetically-tested embryos for replacement in the uterus.

46. A special feature of PGD is the tentative creation of human embryos not as an end in itself but as a means to "ensure" the birth of a healthy child. In this sense, PGD is an enabling technology where one category of embryo is discarded and another category is allowed to become a child and a full member of society. In PD, a comparable choice is made by selective abortion, but here conception occurs in a natural way.

47. Among clinical geneticists there has been much discussion about the main goal of PD. Some have argued that the main aim is to avoid the birth of an affected child. Others have emphasized the reproductive confidence and the purpose of informing couples at risk about the status of the foetus. Several studies indicate that if there is no PD option a large proportion (up to 50%) of couples at high risk (15-25%) of an affected child refrain from pregnancy despite their wish to reproduce. When PD is possible many more at-risk couples (up to 90%) dare to embark on a pregnancy.

48. It has been argued that the selection process in PGD lacks the psychological barrier of having to decide about terminating a pregnancy as in PD. This might lead more easily to an extension of the selection process to other characteristics of the embryo than the presence of a

specific genetic abnormality. Examples are testing and selection for gender and maybe other normal characteristics and HLA typing for fitness as a future donor of tissues or organs for a sibling with a life-threatening disease (see Section 5b).

49. It is not possible to make general statements about the psychological impact of the decisions involved in PD and PGD. After PD, couples may be confronted with the difficult decision of whether or not to terminate the pregnancy. The later a termination is performed, the more stressful it is. It has been well documented that the termination of a desired pregnancy when an affected foetus is detected by PD results in temporary sadness or depression with great individual variations. It is also known that nearly all couples who undergo PD and abortion request another PD if they become pregnant again.

50. A small proportion of couples who have experienced repeated abortions ask for referral for PGD. Within the PGD group this comprises about 21% of the referrals. The perception of couples in making decisions about selection, transferral and the fate of supernumerary normal and abnormal embryos varies considerably. The same is true concerning this attitude in case of failure.

51. After selection and transferral of 1-2 embryos, a vital pregnancy will occur only in 20-25% of cases and the birth rate of a child is even lower. In order to give birth to a healthy child after PGD, most women therefore have to undergo IVF and PGD several times. It has been documented that in cases of IVF failure the psychological consequences can be serious and in some cases requires professional help.

52. More subtle differences between PD and PGD concern the process of procreation and decision-making involved. In PD, the couple or the woman decides, after the establishment of a pregnancy, whether or not to continue it. In that situation, a relationship with the developing child may already exist and influence the woman's or the couple's decision. They may still decide to continue the pregnancy. In PGD, the decision in favour of selection is done before medical treatment is started; it therefore becomes a constitutive part of procreation.

5. Extension of Indications for PGD

a. Sex Selection

53. The first published example of PGD concerned sex determination in a couple at risk of an X-linked genetic disorder, where only males may be clinically affected. Since then DNA research has revealed the responsible mutations for various X-linked disorders so that sexing of the embryo is less relevant.

54. In the meantime the third ESHRE report (2002) has revealed that three centres reporting to the consortium have performed over 70 cycles and PGD for sex chromosomes because of non-medical reasons. The term used is "family balancing" but this does not change the fact that 8-cell embryos of a specific sex are discarded for non-medical reasons. It is likely that commercial centres are increasingly involved in sex selection (see also Chapter IV).

55. On the basis of cultural and/or socio-economic background, in several parts of the world there is a strong preference for male children. At present PD by chorionic villus sampling and direct foetal sexing or early ultrasonography are means to determine the foetal sex allowing couples to abort a foetus of a non-desired gender. As soon as PGD technology is available it will certainly be used for this purpose as well, although only by a small elite that can financially afford it.

56. According to the ESHRE report 70% of the participating centres oppose to the idea of embryo sexing and authoritative clinical geneticists have made a plea to limit PGD to medical indications.

b. Immunogenetic Typing

57. A recent example of extension of the indications for PGD has been the HLA typing of blastomeres. Some forms of leukaemia or genetic blood diseases that are fatal when untreated can be cured by transplantation of normal bone marrow cells. For a bone marrow transplantation to be successful the donor cells must be immunogenetically (as tested by HLA markers) identical to those of the recipient. Especially in small families the chances are small that an HLA matched sibling or parent is available.

58. In two such situations the parents of an affected child have requested PGD not only for the disease concerned but in addition for an HLA test to select 8-cell embryos that have a suitable immunogenetic match to act as a donor. Here there is a combination of PGD for medical reasons (testing for a specific blood disease) and typing for a non-medical characteristic i.e. fitness to donorship. The first is in the interest of the prospective child, the second does not benefit the child but may be life saving for an affected sibling. In the United States of America a child with Fanconi anemia has been cured by transplantation of stem cells present in the cord blood of a newborn who was conceived under PGD conditions as described above.

6. Ethical Considerations

59. In dealing with PGD, the International Bioethics Committee (IBC) recognizes that several general ethical considerations need to be taken into account, concerning for instance the status of the human embryo, the selection and destruction of human embryos, or the health implications for women. In particular, the IBC has reported in detail on the philosophical, socio-cultural and religious issues related to the status of the human embryo in its report on "The Use of Embryonic Stem Cells in Therapeutic Research" (2001). Paragraphs 22-36 of the abovementioned report, are therefore relevant to the present ethical considerations.

60. As is the case in many other international and advisory groups it is not possible to make a generally-accepted statement about the moral acceptability of PGD. Several different positions for philosophical, socio-cultural or religious reasons can be identified:

a) PGD is ethically unacceptable on whatever indication because:
   - it is considered that a human being, defined by some as a person, comes into existence at the time of fertilization;
   - it is considered that PGD requires tentative creation of human embryos for selection;
   - it is considered that PGD puts too much burden on the woman.

b) PGD may be ethically acceptable under specific conditions because:
   - it is considered that the full status of a human being is acquired gradually during intrauterine development;
   - it is considered that the embryo is ensouled at some stage during intrauterine life;
   - it is considered that the well being and health of the mother-to-be and prevention of suffering of the future child justifies the procedure.

61. In the light of such heterogeneous positions, a pluralistic approach is chosen as in the report on "The Use of Embryonic Stem Cells in Therapeutic Research" (2001). As in the case of research on embryonic stem cells or termination of an early pregnancy on the basis of prenatal diagnosis, each society should determine what appears to be an acceptable position towards PGD and regulate the issue accordingly.

62. More generally, concern has been expressed that the emphasis on avoiding the birth of an affected child will have a negative effect on our perception and care of handicapped children who are born. However, in developed countries in terms of budget and care there has never been so much attention given to the care for the handicapped as today.

63. It is difficult to evaluate whether the existence of new technologies like IVF and PGD puts extra pressure on couples to have children. One can also point to the greater reproductive choice couples at genetic risk have thanks to the availability of those new technologies.

64. It should be emphasized that there is a strong imbalance of burden-sharing between the two partners: it is the women who carry the physical and most of the psychological burden of the procedures in an attempt to overcome infertility and/or genetic problems.

65. An often-debated subject is line-drawing in case of the indications both for PGD and PD. So far all professional organisations in clinical genetics and reproductive technology and all advisory groups on bioethics have argued against lists of diseases that can be defined as severe enough to justify PGD or PD. The number of monogenic diseases alone exceeds 5,000 and nearly each of these has variants of different severity and clinical course. Also the same disease may be perceived differently by different couples depending on their family history, religious and socio-economic background, life situation and future expectations.

66. It has also to be kept in mind that decisions about natural reproduction are not subject to social control; it is known that couples embark on a pregnancy for a variety of reasons, several of which might not be beneficial for the well-being of the future child. In medically-assisted reproduction, however, doctors have to justify the intervention according to their professional values and norms.

67. In the case of assisted reproduction technology the professionals involved do have a responsibility especially for proper genetic counselling, informed consent, quality control and clear information about the possibilities and limitations of the technology. As far as the indications are concerned most experts have pleaded to limit PGD to medical reasons.

68. Destruction of embryos for non-medical reasons or termination of pregnancies because of a specific gender are not "counterbalanced" by avoiding later suffering by a severe disease. Sex selection by PGD or PD is therefore considered to be unethical.

69. In the case of HLA typing, in addition to PGD for a specific (blood) disease, a normal characteristic of the embryo is investigated but the purpose is a medical intervention for somebody else, later on. After publication of the first clinical example of PGD and HLA typing in 2001 the term "designer-baby" has been used to highlight ethical reservations towards an instrumental use of PGD. In this context it should be noted that parents of an affected child might want a pregnancy anyway and ask for PGD in order to avoid PD and possible abortion. HLA typing of amniotic fluid cells or chorionic villi and subsequent abortion in case of a non-matched foetus is considered unethical. Once PGD is granted for a specific disease it is difficult to raise moral objections against additional HLA typing to save the life of a sick sibling. PGD with the only goal of HLA typing and selecting embryos fit for donorship after birth is, however, considered unethical, since the embryo becomes instrumentalized for the benefit of others.

70. There have been exceptional requests by couples who themselves are affected by a genetic disease (deafness, dwarfism by achondroplasia) to perform PGD and select embryos carrying the same mutation for transfer to the uterus. In this way an affected baby would be conceived on purpose with the idea that such a child would better integrate in the family. The International Bioethics Committee of UNESCO (IBC) considers such an approach to be unethical because it does not take into account the many lifelong and irreversible disadvantages that will burden the future person.

71. The literature on psychological and behavioural aspects of PGD is relatively scant. Are parent/child relatives influenced by the choices prospective parents make about their offspring? Do parents have higher expectations after selection of embryos for specific biological characteristics? More generally, the issue was raised whether a child's "open future" is sacrificed through an uncompromising respect for parental liberty in reproductive decisions, including avoidance of potential harm.

72. An important issue is the possible effect of embryo selection on the parents perception of children born after PGD. Do their expectations of a child's development and performance differ from those after a natural conception? Since a person's identity and sense of self are at least partially a product of social interactions, does the knowledge of being selected in vitro affect parent-child relationships?

IV. ANEUPLOIDY TESTING TO IMPROVE IVF RESULTS

73. As long as in vitro fertilisation (IVF) is being practised in case of infertile couples its low success rate in terms of children born and the frequent occurrence of multiple pregnancies have concerned both professionals and couples. In time the number of 8-cell embryos that were transferred to the uterus has decreased because of negative experiences with multiple pregnancies, premature births and associated complications for the children. Most fertility clinics now transfer two embryos selected in vitro by morphological criteria; some already transfer one embryo only.

74. Various studies on spontaneous abortions have shown that more than half are associated with chromosomal abnormalities at the early stages of the embryo. With the development of PGD it became possible to test 1-2 blastomeres for certain chromosomal abnormalities. Using specific fluorescent-labelled DNA probes, the most common chromosomal abnormalities like trisomy 21 (Down syndrome), trisomies 13, 16, 18 and 22 and numerical abnormalities of the sex chromosomes X and Y can be tested (aneuploidy testing).

75. One of the common indications for PGD-aneuploidy testing is a combination of infertility and advanced maternal age, which in itself is associated with an increased risk of certain chromosomal abnormalities. Other indications have been recurrent abortions and repeated IVF failures after transfer of morphologically normal embryos.

76. During recent years aneuploidy testing has been increasingly performed in cases of IVF without increased risk of affected offspring. The expectation is that, by selecting and transferring embryos shown to lack the tested chromosomal abnormalities, the chance of becoming pregnant increases and that of having a miscarriage decreases. It is also hoped that in the future transfer of one well-selected embryo will be sufficient and problems of multiple pregnancy will be avoided.

77. Although retrospective studies without proper controls seem promising, reliable prospective studies are needed to provide evidence of the clinical value of aneuploidy testing. For those who accept PGD and PD as a means to avoid the birth of an affected child there

seem to be no moral objections against aneuploidy testing aimed at improving the efficacy of IVF and at the same time preventing the development of a child with an abnormal chromosome pattern.

78. The third report of the ESHRE Consortium (2002) indicates that in Europe 13 out of 20 centres perform aneuploidy testing. In the United States of America there is increasing activity in this field. This seems especially important in view of the high rate of multiple pregnancies in this part of the world as a result of the higher number of embryos that are transferred.

V. GERM-LINE INTERVENTION

79. Germ-line interventions aim at the correction of a specific genetic abnormality in the germ cells or early embryo or at the introduction of genes that may confer to the embryo additional traits like increased resistance to certain diseases. Spermatozoa cannot be used for diagnosis or genetic correction because these procedures would at the same time result in the destruction of the germ cell. Oocytes have a so-called polar body that in principle could be used for diagnosis of gene abnormalities that are transmitted along the female line.

80. Technically there are currently no ways to correct a genetic defect in germ cells and the progress of research in this field is very modest. A major obstacle is that the introduction of genes cannot be controlled and random incorporation of foreign genetic material may well lead to unwanted effects at the cellular level and may harm the developing embryo, foetus and child.

81. Furthermore any genetic change of germ cells or early embryos may be passed to future generations, which may imply irreversible risks. Given these facts, the complexity of the relationships between genes and environment and the notion that some genes associated with disease may be beneficial in another context, the most elementary prudence requires that germ-line intervention should not be undertaken on the basis of the “precautionary principle”.

82. If the safety of germ-line intervention could be guaranteed in the future there is still the alternative of selecting normal embryos by PGD as described in Chapter II. If selection of embryos were unacceptable and germ-line intervention were preferred, the complexity of the procedure would limit the beneficial effects to a very small group of people. The idea raised in some discussions that germ-line intervention would enable the elimination of “harmful” genes from entire human populations is more utopian than realistic.

83. On ethical grounds most national and international institutions have strongly discouraged or prohibited germ-line interventions. In many considerations it also plays a role that a distinction between “therapeutic” purposes and “enhancement of normal characteristics” is far from being clear. Future insights and new technologies may enable intervention aimed at “good” and “bad” human traits and raise fundamental moral questions (see Chapter VI).

84. A considerable number of States as well as supranational institutions have adopted legislation or recommendations against the use of germ cell intervention (see Annex II). The Universal Declaration on the Human Genome and Human Rights states in Article 24 that “germ-line interventions could be contrary to human dignity” and there is no reason to date to modify this position.

VI. FUTURE DEVELOPMENTS AND DILEMMAS

85. The development of new technology during the past two decades has led to a shift in the perception of the purpose of medically assisted reproduction. IVF aims at having a child, PGD aims at having a healthy child and PGD/HLA testing aims at having a healthy and helpful child. Undoubtedly research and technology related to genetics will further develop in the years to come and will also provide new opportunities for couples to select their offspring. In this Chapter the possibilities and dilemmas related to the testing for genes associated with an increased risk of multifactorial diseases in adulthood (susceptibility genes) and the issue of testing for normal physical and mental characteristics will be discussed.

1. Testing for susceptibility genes

86. Until now the main emphasis in clinical genetics has been on congenital malformations and genetic diseases associated with chromosomal abnormalities or mutations in single genes. Most diseases in adulthood however, such as cancers, cardiovascular disorders, diabetes, rheumatoid arthritis, several psychiatric diseases and neurodegenerative disorders including dementias are caused by a complex interaction of several genes and environmental factors including life style. Because of the high incidence and social importance of these diseases, genetic research and its clinical application are increasingly directed towards multifactorial diseases of adulthood.

87. Already many DNA sequences are being identified that are linked to an increased or decreased risk of developing a specific disease. Examples of gene mutations related to a high (60-90%) risk are those for breast cancer and colorectal cancer. Many other specific DNA sequences double or quadruple the population risk, which in itself varies considerably. Examples include venous thrombosis, diabetes, manic depression and certain forms of Alzheimer dementia.

88. With improving insights and technology, especially the development of DNA chips, which enable the simultaneous analysis of tens of thousands of DNA sequences it is likely that testing for combinations of genes will become possible even at the level of 1-2 cells like in PGD.

89. A major dilemma will be whether it is ethically acceptable to test and select embryos for an increased risk of developing a particular disease later in life. Some authors have pleaded to restrict PGD to severe diseases, others have pointed out that it is impossible to exactly define a “severe disease”. Here not only the clinical features and the risk of mortality and chronic handicap are at stake, but also the perception of severity by the couples involved. In many instances couples requesting PGD already have experience with a particular disease in their own family.

90. Testing for susceptibility genes does not, however, imply a diagnosis or certainty that the embryo will later be clinically affected, but only an estimation of a risk. Is a risk in itself an indication for testing and selecting embryos? Some experts have expressed fear that in the long run every embryo and person will appear to be genetically at increased risk for some medical condition, so where is the limit? Others defend that only couples who are very motivated by family experience will request testing for susceptibility genes. In fact there have already been a few requests for PD by women who carry one of the high-risk breast cancer gene mutations, but the health professionals involved have so far not reached an agreement on this issue.

91. In our Committee there is also no unanimous opinion about the acceptability of testing for susceptibility genes. It is considered too early to express a conclusion because of the as yet limited scientific and clinical data and the scarcity of debate both among professionals and the public. It is, however, felt that testing for risk genes associated with diseases in (late) adulthood has a low priority in PGD, although future applications are not categorically rejected. If applied, this testing should be restricted to couples with a high genetic risk of severe diseases and a hard family history.

92. By testing for multiple genes, related to disease or normal characteristics, we undoubtedly approach the "designer baby" and the earlier remarks about the loss of an "open future" for children (see Chapter II.6) and adults seem of extra importance. In this context it should be underlined that the future functioning of an individual results from a complex interaction of genetic and environmental factors. Also, it will be difficult to predict which "ideal characteristics" will be required in future societies.

2. Enhancement of normal characteristics

93. Most but not all professionals involved would endorse that PGD and PD be limited to medical indications. Fertility clinics where sex selection is performed for non-medical reasons apparently have a different view and would argue that the psychosocial disadvantage for a specific gender or the need of "family balancing" justifies the procedure.

94. The IBC endorses limiting PGD to medical indications. However, it is recognized that the distinction between medical indications and typing for normal characteristics is not always clear. One illustration of this would be the testing for normal immunological characteristics and subsequent attempts at enhancing some of these so as to prevent infectious diseases in later childhood. Another example would be the enhancement of later growth in case of a risk of remaining very small.

95. It is easy to describe a slippery slope of searching for genes related to a variety of normal characteristics and either selecting embryos with "the best constitution" or enhancing those characteristics considered to be desirable. Although such scenarios are not within technical reach there have already been reports on DNA sequences linked to human behavioural characteristics. In this respect, the importance of education, living conditions and environment must be stressed (see par. 92).

96. In many public debates fear is being expressed that in the future it will be possible to screen for characteristics such as stature, baldness, obesity, skin and hair colour, intelligence, musicality and specific abilities required for top sports. Without further elaboration our Committee rejects the idea of testing and/or enhancing any human characteristic other than those of importance in alleviating suffering by disease.

97. With regard to germ-line interventions, the most fundamental argument is that we do not have the right to predetermine characteristics of future generations. The notion of justice between generations, defended by philosophers from completely different backgrounds, demands respect for the living conditions of future individuals who should be free to develop their potentialities without being biologically conditioned by the particular conceptions of "good" and "bad" human traits that were dominant at the time they were conceived. Neither PGD nor genetics in general should become instruments for "intergenerational tyranny".

98. Another argument against genetic enhancement of normal human characteristics is that it would profoundly affect our self-perception as "persons" - that is as autonomous beings. Instead we might consider ourselves to be mere "things" or biological artefacts designed by others.

99. A final objection against testing for normal characteristics, selection and enhancement is that even if social agreement on the "ideal" human being is reached, it will inevitably reinforce stigmatisation and discrimination of those who do not fall into the accepted standards of genetically desirable traits. And who is able to define now the ideal human characteristics for the future?

VII. CONCLUSIONS

100. On the basis of the above considerations, the International Bioethics Committee (IBC) has therefore reached the following conclusions:

- Correction of a specific genetic abnormality in germ cells or early stage embryos (germ-line intervention) has not yet been carried out in medical practice. Because of the many technical problems and uncertainties about possible harmful effects on future generations, germ-line intervention has been strongly discouraged or legally banned.
- Pre-implantation genetic diagnosis (PGD) may be an additional option for parents at increased risk of giving birth to a child with a genetically caused disease or malformation.
- Despite a decade of clinical use, PGD is still considered an experimental procedure requiring highly specialized skills and a multidisciplinary approach. So far several dozen centres in wealthy countries have applied PGD in a few thousand couples at risk and a few hundred healthy babies have been born.
- Given the different ethical views about the value of human prenatal life, the IBC cannot make a general statement about the moral acceptability of PGD; instead it has taken a pluralistic approach comparable to that in the Report on "The Use of Embryonic Stem Cells in Therapeutic Research" (2001).
- In most cases the reproductive history, risks and the demanding procedure of PGD will prevent couples from making unjustified decisions about their future offspring. The appropriate use and possible misuse of PGD technology should be debated. At a national level, protocols of PGD, including the process of information and consent of the couples involved, should be reviewed.
- More psychosocial studies are needed to evaluate the possible pressure originating from the availability of new technologies like PGD, the possible influence on the parent-child interactions as a result of high expectations after embryo selection and the effect of PGD on couples because of greater reproductive choice. Also the possible impact on disabled people and their parents should be considered.
- It is recommended that PGD be limited to medical indications. Therefore sex gender selection for non-medical reasons is considered to be unethical.
- Embryonic HLA typing for fitness as a donor of blood stem cells after birth to save the life of a sibling with a genetic blood disease or leukaemia is considered ethically acceptable only if it is carried out simultaneously with PGD for the disease concerned and if mismatching of the HLA type is not considered in itself as a basis for selecting against the embryo unaffected by the disease concerned.

- PGD to select and implant embryos with a similar genetic disease or condition as (one of) the parents is considered unethical.
- PGD of chromosomal abnormalities to enable selection and implantation of unaffected embryos thereby possibly improving the results of in vitro fertilisation (so-called aneuploidy testing) is considered ethically acceptable. Because of its high cost the technology of PGD is presently not equally available to couples that need it.
- A decision about the acceptability of PGD for DNA sequences that are associated with an increased risk of multifactorial diseases, including many forms of cancer, cardiovascular disease and neurodegenerative disorders, requires more public debate and discussion among professionals. If such forms of PGD were considered, they should be restricted to cases involving high genetic risk and clinically severe diseases.
- The recommendation that PGD be limited to medical indications implies that testing for normal physical and mental characteristics is rejected. The same applies to germ-line intervention.

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ANNEX I

COMPOSITION OF THE IBC WORKING GROUP ON PRE-IMPLANTATION GENETIC DIAGNOSIS AND GERM-LINE INTERVENTIONS

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ANNEX II

Some Guidelines and Legislation on Germ-line Intervention

INTERGOVERNMENTAL ORGANISATIONS

Council of Europe. *Convention on Human Rights and Biomedicine,* 1997, art. 13.

> "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." (art. 13)
>
> "Whilst developments in this field may lead to great benefit for humanity, misuse of these developments may endanger not only the individual but the species itself. The ultimate fear is of intentional modification of the human genome so as to produce individuals or entire groups endowed with particular characteristics and required qualities." (Explanatory Report to the European Convention, point 89)

European Union. Group of Advisers on the Ethical Implications of Biotechnology to the European Commission, *Opinion n° 4 on the Ethical Implications of Gene Therapy,* December 13, 1994.

> "Because of the important controversial and unprecedent questions raised by germ-line therapy, and considering the actual state of the art, germ-line gene therapy on humans is not at the present time ethically acceptable." (point 2.7)

NON-GOVERNMENTAL ORGANISATIONS

CIOMS (Council for International Organizations of Medical Sciences), *Declaration of Inuyama on Human Genome Mapping, Genetic Screening and Gene Therapy*, 1990.

> "Before germ-line therapy is undertaken, its safety must be very well established, for changes in germ cells would affect the descendants of patients."

Council for Responsible Genetics, *Paper on Human Germline Manipulation*, 1992.

> "There is no universally accepted ideal of biological perfection. To make intentional changes in the genes that people will pass on to their descendants would require that we, as a society, agree on how to classify 'good' and 'bad' genes. We do not have the necessary criteria, nor are there mechanisms for establishing such measures. Any formulation of such criteria would inevitably reflect particular current social biases. The definition of the standards and the technological means for implementing them would largely be determined by economically and socially privileged groups (...).
>
> The following arguments lead us to unequivocally oppose germline modification:
> (1) Germline modification is not needed in order to save the lives, or alleviate the suffering, of existing people. Its target population are "prospective people" who have not even been conceived.

(2) The cultural impact of treating humans as biologically perfectible artefacts would be entirely negative. People who fall short of some technically achievable ideal would be seen as "damaged goods", while the standards for what is genetically desirable will be those of the society's economically and politically dominant groups. This will only increase prejudices and discrimination in a society where too many such prejudices already exist.
(3) There is no way to be accountable to those in future generations who are harmed or stigmatized by wrongful or unsuccessful germline modifications of their ancestors.

The Council for Responsible Genetics therefore calls for a permanent ban on germline gene modification."

NATIONAL LEGISLATION

Australia. National Health Medical Research Council (NHMRC). *Guidelines for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies*, 1999 (http://www.nhmrc.health.gov.au/issues/humangenetics.htm).

"While the introduction of DNA or RNA into somatic cells is ethically acceptable, the introduction of DNA or RNA into germ (reproductive) cells or embryos is ethically unacceptable, since there is insufficient knowledge about the possible consequences including hazards and effects on future generations (...). HRECs [Human Research Ethics Committees] would not be expected to receive, and should not approve, research proposals for the introduction of DNA or RNA into germ (reproductive) cells or embryos" (*Introduction*).

Brazil. *Law n° 8974 on Genetically Modified Organisms*, 1995, art. 13.1.

"The following acts shall constitute crimes:
1. the genetic manipulation of human germ cells."

Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, 1998, art. 8.5. (http://www.nserc.ca/programs/ethics.htm).

"Gene alteration (including 'gene therapy') that involves human germline cells or human embryos is not ethically acceptable. Gene alteration for therapeutic purposes and involving human somatic cells may be considered for approval."

Denmark. Danish Council of Ethics, *Humans and Genetic Engineering in the New Millenium*, 1999 (http://www.etiskraad.dk/english/).

"(...) there has also been an international consensus to date among researchers and politicians that gene therapy is only to be conducted on the gravely ill, and only on their somatic cells that will not be passed on to the next generation."

France. *Civil Code*, art. 16-4 (introduced in 1994); National Advisory Committee on Ethics, *Opinion n°22 on Gene Therapy*, December 13, 1990.

> "Without prejudice to research seeking to prevent or treat genetic diseases, no alteration can be made to genetic characteristics with the aim of modifying a person's offspring." (Civil Code, art. 16-4)
>
> There must be formal prohibition of any attempt to perform germinal gene therapy." (French National Advisory Committee on Ethics)

Germany. *Embryo Protection Law*, 1990, art. 5.

> "Article 5
> (1) Any person who artificially alters the genetic information of a human germline cell shall be punished by up to five years' imprisonment or by a fine.
> (2) The same penalty shall be imposed on any person who uses a human germ cell with artificially modified genetic information for fertilisation."

Switzerland. *Constitution*, art. 119a.

> "Any form of human cloning and any intervention in the genetic information of gametes and human embryos are forbidden."

United Kingdom. *Human Fertilisation and Embryology Act*, 1990, Schedule 2, arts. 2(4), 3(4); *Report of the Committee on the Ethics of Gene Therapy* (Chairman: Cecil Clothier), 1992; British Medical Association, Ethics Committee, *Human Genetics. Choice and Responsibility*, Oxford University Press, 1998, p. 198-199.

> "A [treatment] licence ... cannot authorise altering the genetic structure of any cell while it forms part of an embryo." (Human Fertilisation and Embryology Act, 1990)
>
> "We are clear that there is at present insufficient knowledge to evaluate the risks to future generations of gene modification of the germ line. We therefore recommend that gene modification of the human germ line should not yet be attempted." (Committee on the Ethics of Gene Therapy)
>
> "Alternation of a defective gene in the germ cell or in the early embryo would enable future generations to benefit from the treatment but its safety is not, and in the short term cannot be, proven. In view of these concerns, there is widespread agreement that germ cell gene therapy should not be undertaken." (British Medical Association)

United States of America. NIH, *Guidelines for Research Involving Recombinant DNA Molecules*, 1998, Appendix M (http://www.niehs.nih.gov/odhsb/biosafe/nih/rdna-apr98.pdf).

> "RAC [Recombinant DNA Advisory Committee] will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer."