



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
Paris, 30 September 2002
Original: English

Draft Report on Pre-implantation Genetic Diagnosis and Germ-line Intervention

**WORKING GROUP OF THE IBC ON
PRE-IMPLANTATION GENETIC DIAGNOSIS AND GERM-LINE INTERVENTION**

Rapporteur: *Hans Galjaard*

Division of the Ethics of Science and Technology

I. INTRODUCTION

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


2. Moreover, in its recommendations adopted at the 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), which met at Headquarters, Paris, on 23 and 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).

4. It should be recalled that certain previous reports prepared within the framework of the deliberations of the IBC are of particular interest to the subjects under consideration. These are in particular 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 the past decades fundamental research in genetics has developed at increasing pace. In human genetics new insights in the molecular background of diseases and new technologies, especially of DNA analysis, have also enabled the early and exact diagnosis of an increasing number of congenital disorders, the identification of parents at increased risk of affected offspring and genetic counselling.

6. In most wealthy countries a new medical discipline, clinical genetics, has been incorporated in 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 affected offspring  undergo chorion villus sampling (around 11th week of pregnancy) or amniocentesis (16 weeks) and, after cultivation of fetal cells, chromosomal, biochemical or DNA analysis may reveal whether the unborn is affected by one of the specifically tested abnormalities. If this is the case the prospective parents may decide to terminate their pregnancy thereby avoiding the birth of an otherwise severely affected child.

7. An alternative, non-invasive method of prenatal diagnosis is ultrasound examination which will reveal major structural and sometimes functional fetal abnormalities  though usually later in pregnancy.

8. There is general agreement about the major indications for prenatal testing, most women in Western countries know about its possibilities and the costs are covered by public means c.q. health insurers.

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

10. The technique is based on IVF, division to 8-cell stage embryos, biopsy of 1 or 2 cells, analysis by DNA technology for specific abnormalities and selection of non affected embryos for transfer to the uterus.

11. The first pre-implantation genetic diagnoses (PGD) were published around 1990 and since then a few dozens of centres have acquired the highly specialized, multidisciplinary expertise needed. In Europe and North America several thousands of PGD have been established and several hundreds (healthy) babies were born. PGD's for at risk couples have so far been performed for major chromosomal aberrations and some thirty different monogenic diseases. It is likely that in the (near) future the scope of PGD will be widened to many other conditions, including genetic susceptibility for major diseases in adulthood.

12. During the last years it has become more and more customary to test 6-8 cell embryos collected for "traditional IVF" in infertile couples, for chromosomal abnormalities and to transfer only 1-2 embryos which are 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. A number of centres also accept sex selection under certain conditions and most recently there have been a few examples of selecting embryos with the necessary immunogenetic characteristics to function after birth as a donor of blood stem cells to save a brother or sister with a fatal genetic disease or leukaemia which can only be cured if compatible hemopoietic stem cells for transplantation are available.

14. The last three examples of application of PGD are no longer related to the "conventional forms of prenatal diagnosis" with the aim to avoid severe congenital disorders. Instead the purposes are of a technical nature (improve results IVF), a social character (preference of male or female child) or the use for later donorship.

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

III. PREIMPLANTATION DIAGNOSIS (sensu stricto)

1. Methodology

16. The basis of PGD is the in vitro fertilisation 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. The number of cycles per woman varies greatly (1-8) and an average of 12 oocytes are retrieved per cycle.

Fertilisation with sperm of the husband is performed and about 70% of the oocytes will fertilise. 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 an 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%.

18. Depending on the indication specific tests are performed to detect abnormalities at the gene or chromosomal level. At present the most often used 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. At this moment limited experience has been gained for about 30 different monogenic diseases and the number of misdiagnosis as revealed by follow-up studies has been of the order of 1%.

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 fetal loss, premature birth and its complications. Even after transfer of 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 a mean of two cycles. At day 10-14 a hormone test is performed to check whether the transferred embryo(s) has implanted and at 7 weeks ultrasonic control of the fetal heart action is carried out. Since PGD is still considered as an experimental procedure a follow up of the early diagnosis is recommended by "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 but the diagnostic disadvantages that only maternally inherited problems can be detected and that not all unaffected subsequent embryos can be identified.

22. It has also been attempted to perform genetic analysis at a later stage of embryo development i.e. the blastocyst stage of circa 100 cells which is 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 but a major drawback is that very few embryos reach this stage under in vitro conditions. So far there is no clinical experience of PGD after 5-6 days of culture.

23. Some follow-up studies of babies born after PGD have revealed an increased risk of the normal incidence of congenital malformations at birth other studies did not indicate an increased risk. Clearly more well controlled follow-up studies have to be performed before a definite answer can be given.

24. For each new indication the procedure of PGD has to be tested experimentally and as a result couples at risk of a specific rare genetic disease often have to 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 who have a high risk of genetically abnormal offspring in addition to an infertility problem;
- couples at high genetic risk who have undergone “conventional” prenatal diagnoses and had to terminate recurrent pregnancies after the finding of an affected fetus;
- couples who have objections against termination of pregnancy.

26. In addition couples at advanced age referred for IVF because of infertility may ask for PGD of chromosomal aberrations (see section 5a).

27. One group at increased risk of affected offspring involves parental carriership of a balanced chromosome translocation. In this situation the risk of severely affected offspring with an unbalanced chromosomal aberrations may be very high.

28. In fewer instances a risk of a numerical chromosomal abnormality because of advanced maternal age will be a reason for PGD (see section III).

29. A third group of high-risk couples are those 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 affected themselves. Their risk of an affected child who inherits the mutation from both parents is 25%. The same is true in the case of an X-linked mutation where the mother is a carrier and sons have a 50% risk of being affected in a disease like Duchenne muscular dystrophy, X-linked mental retardation or haemophilia. In the case of a dominant gene mutation, like in myotonic dystrophy or the late onset Huntington’s disease it is sufficient to have a mutation in one of the chromosomes 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 the number of referrals for an increased risk of chromosomal abnormality is about the same as those at risk of a monogenic disease.

31. During the last year, however the relative number of chromosome analyses related to the normal procedure of IVF 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 usually rare diseases are known to be associated with a single gene mutation and 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 PGD.

3. Organisation and Regulation

32. PGD requires a multidisciplinary approach. Usually referral to a fertility clinic will take place after genetic counselling in a clinical genetics centre. In case one of the parents, one or more children or close relatives are affected an accurate clinical and laboratory diagnosis must be established to enable proper genetic counselling and to establish an indication for PGD. After referral to the fertility clinic a proper evaluation about the clinical aspects of hormone treatment, oocyte retrieval and IVF must be carried out and the

counselees must be given information about these clinical aspects as well as the possibilities and limitations of the IVF and PGD procedures. Evidently the procedure of selection of 8-cell embryos must be thoroughly discussed as well as the fate of abnormal embryos, supernumerary unaffected embryos. Especially important is information about the relatively low yield of success in terms of the birth of an unaffected baby and of course the disadvantages of a multiple pregnancy.

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

34. It is clear that the complexity of the multidisciplinary approach has thus far limited the application of PGD. The European Society of Human Reproduction and Embryology (ESHRE) has formed a PGD Consortium in 1997. Goals were 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 about 1560 referrals during the past three years. Recently the number of participating centres has increased to 32.

35. About one quarter of the couples has one or more affected children and an even larger percentage had 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 from the 21 centres that replied were against it.

36. For a multidisciplinary approach of PGD close collaboration between the various units and professionals is to be preferred. In about half of 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 800 miles apart 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 the quality control both of the clinical and laboratory methods and of the indications for PGD used.

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 about indications and quality control. In France, Spain, Sweden and the United Kingdom legislation of PGD has been implemented. In Belgium, 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 in many instances public funding is available via insurers or national/regional governments. For the clinical use of PGD consent of local ethical committees is required and 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 (1996) states in article 36 that countries that 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 like Austria, Germany, Ireland and Switzerland, PGD is not allowed; in Australia some States (like Western Australia) have prohibited PGD whereas 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 that want PGD are confronted with high costs. In different publications the estimates for PGD vary from \$15,000 to more than \$100,000 depending also on the number of cycles involved. As a consequence in the United States of America PGD seems accessible only for couples at risk who are in a financially strong position.

4. Comparison PGD with “conventional prenatal diagnosis”(PD)

42. Most experts consider PGD as an additional option for couples at increased genetic risk  not as a replacement of “conventional prenatal diagnosis” (PD) by amniocentesis or chorion villus biopsy.

43. A major technical difference is that PGD is still considered as a highly specialized experimental procedure with a limited scope and only a few hundred healthy children have been born during the past decade. PD has a history of clinical application of about 30 years and annually hundreds of thousands couples undergo amniotic fluid (cell) or chorionic villus analyses. A full chromosome pattern and about 1500 usually rare monogenic diseases can be tested whereas in PGD only a limited number of chromosomal abnormalities  and some 30 monogenic diseases can be tested in 1-2 embryonic cells. Amniocentesis may include biochemical testing for open neural tube defects which is not possible in PGD or chorionic villus sampling.

44. Another major difference between PGD and PD is the costs and the accessibility. The costs of PD are of the order of \$580 – few thousand and in most Western countries this will be covered by health insurers since clinical genetics services including PD are incorporated into the health care system. As was mentioned before the costs of PGD varies considerably in different centres and states and also according to the number of cycles and the type of analysis. But in all instances the costs are of the order of \$40,000 to more than \$100,000 and in many instances, especially in the United States of America couples have to pay themselves.

45. Psychologically, PGD and PD are similar in that it offers couples at increased genetic risk an option to reproduce without the risk of the birth of a child with a specific severe congenital abnormality c.q. genetic disease. In PD this approach may be at the cost of terminating a pregnancy at 11- 19 weeks. In PGD abortion is avoided by selecting genetically tested normal embryos for replacement in the uterus. 

46. A special feature of PGD is the tentative creation of human embryo's not as an end in itself, but as a means to establish a “healthy pregnancy”. In this sense PGD is an enabling technology where one category of embryo's are discarded and another category is allowed to become a child and 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 quite some discussion about the main goal of PD. Some have defended that this is the avoidance of 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 option of PD 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 couples at risk (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 deciding about termination of pregnancy as in PD. This lack might more easily lead to 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 5 b).

49. It is not possible to make general statements about the psychological impact of the decisions involved in PD and PGD. It has been well documented that the termination of a desired pregnancy in case an affected fetus is detected by PD, results in temporary sadness or depression with great individual variations. It is also known that nearly all couples who underwent PD and abortion request another PD in case they become pregnant again.

50. A small proportion of couples who have experienced repeated abortions ask for referral for PGD. Within the group of PGD 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 for the attitude in case of failure.

51. In PGD the clinical procedure of IVF is quite cumbersome, but the diagnostic result after IVF is obtained within a few days and decisions by couples at risk professionals are made before pregnancy. After selection and transferral of 1-2 normal embryos a major disadvantage is the great risk of disappointment since only in 20-25% a vital pregnancy will occur and the birth rate of a child is even lower.


52. In PD the diagnostic analyses will be performed at the 11th or between the 16th - 18th week of pregnancy, where a relationship between mother and fetus will have started. In most instances the waiting time for the laboratory diagnosis varies between 2 - 4 days and in case of an abnormal result the decision to terminate a wanted pregnancy is difficult. The procedure of termination is especially stressful at 18 weeks during a short hospital stay.

5. Non Medical 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) reveals 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 do away the fact

that 8-cell embryos of a specific gender are discarded for non-medical reasons. s likely that in the United States of America commercial centres are increasingly involved in sex selection (see also chapter IV).

55. In several parts of the world like Asia and the Middle East there is a strong male preference with a cultural and/or socio-economic background. At present PD by chorionic villus sampling and direct fetal sexing or early ultrasonography are means to determine the fetal sex which allows couples to abort a fetus of non desired gender. As soon as the PGD technology will be available it will certainly be used for this purpose as well though by a small elite who can financially afford it.

56. According to the ESHRE report 70% of the participating centres oppose to the idea of fetal sexing and authoritative clinical geneticists have also 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 which untreated are fatal, 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 of such situations 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. 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 s.s. Therefore a pluralistic approach is chosen like in the report on “The use of Embryonic Stem Cells in Therapeutic Research” (2001).

60. For those like the Roman Catholic Church, who hold the view that all prenatal life after fertilisation is of full and equal moral status to that of all other persons, PGD is ethically unacceptable on whatever indication.

61. For those who consider that the full status of a human being is acquired gradually during intrauterine development with an increasing moral status of the embryo and fetus PGD may be ethically acceptable under specific conditions. The same seems to be true for those who believe that the embryo is ensouled 40 days after fertilisation like in the case of Islam and for those who attach importance to certain physical milestones such as brain development.

62. Like 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.

63. In view of the gradual development of an embryo and fetus and the possible strengthening relations between the mother and her future child PGD seems ethically preferable to PD. However, up to now utilisation of PGD depends as much on the complexity of the procedures as it will on its perceived ethical advantages.

64. More in general 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, both in Europe and the United States of America in terms of budget and care there has never been so much attention for the care of the handicapped.

65. It is difficult to evaluate whether the existence of new technologies like IVF and PGD puts extra pressure on couples to reproduce. One can also point to the greater reproductive choice couples face thanks to the availability of those new technologies.

66. In cases where the desire of a couple to give birth to a healthy child outweighs the burden of the procedures 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 fertility and/or genetics problems.

67. An often-debated subject is line drawing in case of the indications both for PGD and PD. Thus far all professional organisations in clinical genetics and reproductive technology as well as advisory groups on bioethics have argued against lists of diseases which can be defined as severe enough to justify PGD or PD. The number of monogenic diseases alone exceeds 5000 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.




68. In most instances the cumbersome procedures and uncertainties in PGD and the psychological barrier of abortion in PD will prevent people to make unjustified decisions about their future offspring.

69. It has also to be kept in mind that decisions about natural reproduction are without 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.

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

71. 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 as unethical.

72. 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 indicate 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 fetus 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 as unethical.

73. There have been exceptional requests by couples who themselves are affected by a genetic disease (deafness, dwarfism by achondroplasia) to perform PGD and select embryonic cells with the mutation for transfer to the uterus. In this way an affected  by 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 as unethical since it does not take into account the many life long and irreversible disadvantages  which will burden the future person. 

74. The literature on psychological and behavioural aspects of PGD is relatively scant. Are parent – child relatives influenced by the choices prospective parents have to make about their offspring? Do parents have higher expectations after selection of embryos for specific biological characteristics? More in general 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.

75. An issue that is considered of importance 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? And 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 RESULTS IVF

76. 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 been a concern to 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 2 embryos which are selected in vitro by morphological criteria, some already transfer one embryo only.

77. Various studies on spontaneous abortions have shown that more than half of these are associated with chromosomal abnormalities of 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 as well as numerical abnormalities of the sex chromosomes X and Y can be tested (aneuploidy testing).

78. One of the common indications for PGD-aneuploidy testing has been 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 couples with recurrent abortions and repeated IVF failures after transfer of morphologically normal embryos.

79. During the past years aneuploidy testing is increasingly being performed in cases of IVF without any increased risk of affected offspring. The expectation is that by selection and transfer of embryos which are shown to lack any of the tested chromosomal abnormalities, the chance of becoming pregnant increases and that of 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.

80. Although retrospective studies without proper controls seem promising, reliable prospective studies are needed to provide evidence for 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 no moral objections against aneuploidy testing aimed at improving the efficacy of IVF and at the same time preventing the development of a chromosomally abnormal child.

81. The third report of the ESHRE Consortium (2002) indicates that in Europe 13 out of 20 centres perform aneuploidy testing. Also in the United States of America there is increasing activity in this field which 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 is transferred.

V. GERM-LINE INTERVENTION

82. This would imply the correction of a specific genetic abnormality in the germ cells or early embryo to avoid the transfer of a genetically abnormal embryo. 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 which in principle could be used for diagnosis of gene abnormalities which are transmitted along the female line.

83. At this moment technically there are no options to correct a genetic defect in germ cells and also in research work progress 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 to harm for the developing embryo, fetus and child.

84. Furthermore any genetic change of germ cells or early embryo's 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 that are associated with disease maybe beneficial in another context, the most elementary prudence requires that germ-line intervention should not be undertaken on the basis of the "precautionary principle".

85. 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 would not be acceptable and germ-line intervention would be 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 real.

86. On ethical grounds most national and international institutions have strongly discouraged or frankly 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 well enable intervention aimed at “good” and “bad” human traits which would raise fundamental moral questions (see chapter V).

87. A considerable number of States as well as supranational institutions have realized 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 leave this position.

VI. FUTURE DEVELOPMENTS AND DILEMMAS

88. 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. Without doubt 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

89. Up till 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 more and more directed towards multifactorial diseases of adulthood.

90. Already many DNA sequences are being identified which 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 result in a 2-4 fold increase of the population risk which in itself varies considerably. Examples are venous thrombosis, diabetes, manic depression and certain forms of Alzheimer dementia.

91. 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.

92. A major dilemma will be whether testing and selecting embryos for an increased risk to develop later in life a particular disease is ethically acceptable. Some authors have pleaded to restrict PGD to severe diseases, others have pointed out that it is not possible to exactly define what a severe disease is. 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.

93. Testing for susceptibility genes does however not imply a diagnosis i.e. certainty that this embryo will be clinically affected later on, but only an estimation of a risk. Is a risk in itself an indication for testing and selecting embryos? Some experts have expressed the 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 so far did not reach agreement on this issue.

94. Also in our Committee there is no unanimous opinion about the acceptability of testing for susceptibility genes and it is considered to be 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 without categorically reject future applications. If applied it should be restricted to couples with a high genetic risk and a hard family history and to severe diseases.

95. By testing for multiple genes, related to disease or normal characteristics, the “designer baby” undoubtedly comes nearer and the earlier remarks about the loss of an “open future” for a child (see II 6) and an adult of extra importance.

2. Enhancement of normal characteristics

96. Most but not all professionals involved in PGD and PD would endorse a limitation 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.

97. Our Working Group endorses the limitation of PGD to medical indications. It is however 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 with the goal to prevent infectious diseases at later childhood. Another example would be the enhancement of later growth in case of a risk of remaining very small.

98. It is not difficult 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 which are considered to be desirable. Although such scenarios are not within technical reach there have already been reports on DNA sequences linked to male homosexuality, female cognitive features, creativity and risk avoidance and a few other mental characteristics.

99. In many public debates fear is being expressed that in the future it will become possible to screen for a variety of normal characteristics such as stature, baldness, obesity, skin and hair colour, intelligence, musicality and specific abilities required for top sports.

100. 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. 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 also demands respect for human conditions of life 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 of those who preceded them. Neither nor genetics in general should become an instrument for “intergenerational tyranny”.

101. 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 as mere “things” or biological artefacts designed by others.

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

VII. CONCLUSIONS

103. On the basis of the above considerations, the Working Group 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 germ-line intervention has been strongly discouraged or legally banned.
- Pre-implantation genetic diagnosis (PGD) is an additional option for parents at increased risk of a child with a severe congenital handicap based on a chromosomal aberration or a single gene mutation.
- Despite its clinical use during a decade, PGD is still considered as an experimental procedure requiring highly specialized skills and a multidisciplinary approach. Thus far several dozens of centres in wealthy countries have applied PGD in a few thousands of couples at risk and a few hundred healthy babies have been born.
- Given the different ethical views concerning the value of human prenatal life, the IBC cannot make a general statement about the moral acceptability of PGD; instead a pluralistic approach has been chosen comparable to that in the Report on “The Use of Embryonic Stem Cells in Therapeutic Research” (2001).

- In most instances the reproductive history and risks as well as the cumbersome procedure of PGD will prevent couples to make unjustified decisions about their future offspring. The appropriate use and possible misuse of the PGD technology should be debated; at a national level protocols of PGD should be reviewed including the process of information and consent of the couples involved.
- More psychosocial studies are needed to evaluate the possible extra pressure on couples to reproduce because of available technology, the possible negative parent-child interactions as a result of high expectations after embryo selection and of the possible positive effects of PGD because of the greater reproductive choices. The possible negative impact on disabled people and their parents should be considered and optimal medical and social support to them should be guaranteed simultaneously with efforts to prevent birth of severely disabled people.
- It is recommended to limit PGD to medical indications and gender selection for non-medical reasons is considered as 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 as morally acceptable 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 selection against the embryo not affected by the disease concerned.
- PGD to select and implant embryos with a similar genetic disease as (one of) the parents is considered as unethical.
- PGD of chromosomal aberrations enable selection and implantation of non affected embryos thereby possibly improving the results of in vitro fertilisation (so called aneuploidy testing) is considered as morally acceptable. Because of its high costs the technology of PGD is presently not equally available to couples in need of it.
- A decision about the acceptability of PGD for DNA sequences which are associated with an increased risk of multifactorial diseases such as many forms of cancer, cardiovascular disease and neurodegenerative disorders requires more public debate and discussions among professionals. If such forms of PGD would be considered it should be restricted to cases of a high genetic risk, clinically severe diseases and a hard family history.
- The recommendation to limit PGD to medical indications implies that testing for normal physical and mental characteristics is rejected. The same applies to germline intervention.



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



*International Bioethics
Committee (IBC)*

*Comité international
de bioéthique (CIB)*

Distribution: limited

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

Chairperson

KOSZTOLÁNYI Dr (Mr) György (Hungary)
Professor and Chair of the Department of Medical Genetics and
Child Development, University of Pecs
Vice-President of the Faculty of Medicine of the University of Pecs
Former President of the Hungarian Society of Human Genetics

Rapporteur

GALJAARD Prof. (Mr) Hans (The Netherlands)
Professor of Human Genetics
Head of the Department of Clinical Genetics, University Hospital Rotterdam

Members

ANDORNO Dr (Mr) Roberto Luis (Argentina)
Professor of Civil Law

GONÇALVES DOS SANTOS Prof. (Mrs) Heloisa (Portugal)
Professor of Medical Genetics
Head of the Medical Genetics Service, St Maria Hospital, Lisbon
Coordinator of the Bioethics Committee of the Portuguese Society of Human Genetics (SPGH)
Founding Member and Former Chairperson of the SPGH

GUESSOUS-IDRISSI Dr (Mrs) Nouzha (Morocco)
Professor and Head of Parasitology-Mycology Laboratory,
Faculty of Medicine and Pharmacy of Casablanca
Member of the Biomedical Research Ethics Committee, Faculty
of Medicine and Pharmacy of Casablanca
Founding Member of the Moroccan Organization of Human Rights

IDA Prof. (Mr) Ryuichi (Japan)

Professor of International Law

Rapporteur of the Committee of Regional Economic Development Law
of the International Law Association**KIGONGO Prof. (Mr) James Kayolo** (Ouganda / Uganda)

Professor and Head of the Department of Philosophy of the University of Makerere

Chairperson of the National Bioethics Committee of Uganda

KOLLEK Prof. (Mrs) Regine (Germany)

Professor of Health Technology Assessment

Vice-Chairperson of the German National Ethics Council

Former Chairperson of the Advisory Board on Ethics, Federal Ministry of Health

LUONG Dr (Mr) Le Dinh (Vietnam)

Professor and Head, Laboratory of Molecular Genetics, Vietnam National University

Vice-Chairperson and General-Secretary of the Genetics Society of Vietnam

Editor-in-chief of *Genetics & Applications*

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 unprecedented 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 Millennium*, 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.”