Consultation document on preimplantation genetic diagnosis / Human Fertilisation and Embryology Authority and Advisory Committee on Genetic Testing.

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

AND

ADVISORY COMMITTEE ON GENETIC TESTING

CONSULTATION DOCUMENT

ON

PREIMPLANTATION GENETIC DIAGNOSIS

Responses should be addressed to: Ginny Shires
HFEA
30 Artillery Lane
E1 7LS
LONDON
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Introduction

1. This document considers the current and potential use of preimplantation genetic diagnosis (PGD). PGD is a technique whereby embryos created outside the body can be tested to see whether they carry a genetic disorder before being transferred to the uterus. New techniques often cause public unease, especially when it is felt that scientific and medical advances are running ahead of public debate of the social and ethical issues involved. The Human Fertilisation and Embryology Authority (HFEA) is aware that PGD forms part of a complex debate on genetics and the use of genetic information. The HFEA and Advisory Committee on Genetic Testing (ACGT) therefore established a joint group to prepare this discussion document as a basis for considering what guidance should be put in place. The membership of the joint working group is attached at Annex A. Comments are sought to ensure that any such guidance is set in an appropriate ethical framework and reflects both medical and genetics issues as well as the overall acceptability of PGD. A glossary of terms used in this document is provided at Annex E.

What is PGD?

2. PGD was primarily developed in response to requests for help from those at risk of passing on a serious genetic disorder to their children. It is a two stage process in which *in vitro* fertilisation (IVF) is used to create embryos which are then tested for a particular genetic disorder or to establish their sex (where the disorder is sex-linked). Embryos which do not carry the genetic disorder or are not of the potentially affected sex can then be transferred to the uterus in the hope that a normal pregnancy will develop. Annex B provides a description of the science.

Genetic disorders

3. The influences of both genetic and external factors are, to varying degrees, present in all human disorders. Better understanding of these influences offers new opportunities to avoid, prevent or ameliorate the consequences.

4. Many genetic disorders, both congenital and those of later onset, are a consequence of mutations in single genes. Others result from errors involving whole chromosomes (e.g. Down's syndrome), or from the interactions of one or more genes and external factors early in embryonic development. The latter may be the cause of many common congenital malformations (e.g. spina bifida or cleft palate). Interactions between genes and environmental factors seem to be the basis for a proportion of many of the serious diseases that present later in life, including heart disease, diabetes, cancers, and common degenerative diseases. These are known as multifactorial or, where more than one gene is involved, polygenic conditions.

5. Among the serious disorders caused by single gene defects are cystic fibrosis, Duchenne muscular dystrophy, haemophilia, Huntington's disease, the thalassaemias, sickle cell disease, and a number of uncommon hereditary cancers. Although more than 10,000 single gene disorders have been described, most of them are individually rare. It is estimated that around twenty of these disorders account for 70-80% of all the major genetic diseases seen in the UK. The birth prevalence of single gene disorders and chromosomal syndromes is 2% and for all congenital malformations 3%. For many affected couples there is a high risk that the condition will recur in their children.

6. About 1% of cancers are due to specific inherited forms and the techniques of molecular biology can now be used for diagnosis or predictive testing in families at risk. Of potentially much greater impact is the identification of genetic predispositions to common cancers, notability of breast, ovary, colon and prostate. Up to 10% of these cancers may be determined by a single major gene and arise in the context of a strong family history.

The choices facing families

7. Individuals and families known to be suffering from genetic disorders are faced with difficult decisions when considering having children and to date three options have been available:-

a) to decide not to have a child;

b) to opt to have a pregnancy without genetic testing and so "risk" the birth of an affected child (the degree of risk will depend on whether the genetic disorder is autosomal dominant (such as Huntington's disease); autosomal recessive (such as cystic fibrosis and thalassaemia) or X-linked (such as Duchenne's muscular dystrophy). In all cases the probability of having an affected child remains the same for each subsequent pregnancy.

c) to proceed with a pregnancy and have the fetus tested using prenatal diagnosis (PND). If the fetus is found to be carrying a disorder or abnormality the mother then faces a decision whether or not to request a termination (within the provisions of current abortion legislation).

8. For some people termination is not an acceptable option. The prospect of repeating the process of pregnancy and termination one or more times in an attempt to achieve an unaffected pregnancy will be unacceptable to many more.

9. Preimplantation genetic diagnosis, developed in the 1980s, may offer a fourth option for certain families.

The history of PGD

10. PGD has now been practised for several years and has developed because of the availability of *in vitro* fertilisation and new genetic testing techniques. In passing the Human Fertilisation and Embryology Act 1990 (HF&E Act), Parliament made the decision that embryo research should be permitted. The possibility of developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation was recognised at that time. The provision was enacted against the background of a clinical trial which had just been undertaken to establish the technique of pre-implantation genetic

diagnosis in the case of a life threatening sex-linked disorder. The HFEA has accepted the position implicit in the legislation and has licensed PGD for certain severe or life-threatening disorders at a limited number of clinics. Following a public consultation in 1993 the HFEA rejected the use of PGD for sex selection for social reasons[1].

Current Use of PGD

11. Four centres in the UK are currently licensed to carry out PGD and one centre for the embryo biopsy part of the procedure only. The technique was first successfully used in 1990 to produce two sets of twin girls where families were at high risk of passing on a serious X-linked disorder[2]. The first autosomal recessive disorder where PGD resulted in the birth of an unaffected child was cystic fibrosis[3]. Sexing an embryo to avoid X-linked disorders and testing for age related aneuploidy (an abnormal number of chromosomes) are the most common reasons for preimplantation diagnosis world-wide[4]. Testing for cystic fibrosis remains the most common use of PGD for a single gene defect[5].

12. PGD has been used to detect a number of other inherited disorders. These include autosomal recessive disorders, where the specific gene defect is identified, such as Tay Sachs disease and Rh D blood typing. X-linked disorders where PGD, by sex determination, has been used include conditions such as Duchenne's muscular dystrophy and Lesch Nyhan syndrome. With some X-linked disorders, e.g. Duchenne's muscular dystrophy, the specific defect can now be identified in a proportion of families, which means that male embryos free of the disorder can now be implanted along with female embryos. PGD has also been used to test for two autosomal dominant conditions; the gene predisposing to polyposis coli[6] (an inherited cancer of the colon) and Marfans syndrome[7]. As new tests become available this list will continue to grow.

13. A further reason for requesting PGD is where one partner is at high risk of transmitting a chromosome anomaly, such as a translocation. Such couples have often experienced repeated miscarriages and periods of infertility and are already receiving assisted conception treatment. For such patients, PGD may be a way to achieve a successful pregnancy where they would otherwise have difficulty[8]. In some instances, PGD may also

help individuals at risk of having a child with severe developmental problems because of a chromosomal imbalance.

Problems with PGD

14. Several problems can affect the success of PGD. First, there is the possibility of misdiagnosis, either because of a failure of the techniques involved, or because the biopsied material is not typical of the embryo. Furthermore, the biopsy may become contaminated with other non-embryonic genetic material, such as sperm left over from the *in vitro* fertilisation procedure or contaminating cells from the operator.

15. It is essential to the success of PGD that the cell or cells taken from the embryo are wholly representative of the genetic characteristics of the embryo. However, embryos can occasionally be subject to mosaicism in which cells that look similar under the microscope nevertheless have different genetic complements. It is not known how frequently this occurs, but it may lead to misdiagnosis where the biopsied cell is apparently normal, but the remaining cells in the embryo are affected with the genetic defect. The likelihood of misdiagnosis can be reduced if the results are confirmed in more than one cell[9].

16. Another practical problem with PGD is the potential loss of available embryos during a treatment cycle. Besides the usual problems associated with conventional IVF, e.g. failure of fertilisation, some embryos may be damaged during the biopsy, and there will also be those embryos that are found to be affected by the disorder. Experience at two centres has shown that in approximately one third of all cases only one embryo is diagnosed as suitable for transfer. Clearly this may reduce the chance of successfully achieving a pregnancy. Furthermore, the longer term effects of embryo biopsy on child development are not known, although present evidence suggests there are no short term effects. Further follow up studies will be important[10].

17. PGD is dependent on the success of IVF as a technique. The use of PGD by no means guarantees that the treatment will result in a baby being born. The average live birth rate per treatment cycle of IVF in the UK is currently 17%[11] but this figure is affected by a number of factors. Some patients may be older and that will reduce the possibility of

success; on the other hand previous fertility is likely to enhance the possibility of a pregnancy. Similarly the number of embryos available for transfer may also be relevant in determining outcome. The live birth rate for PGD is probably a little lower than for IVF generally.

18. PGD is likely to be more expensive than standard IVF treatment, because of the complex molecular biology and related techniques which are necessary to determine whether the embryos carry the genetic disorder. Thus access to PGD may be limited by the ability of patients to meet the costs themselves, or by the willingness of health authorities to fund the treatment.

19. IVF is a physically and mentally demanding process for couples which does not bring any guarantee of success. The additional considerations described for PGD mean that this is not an easy option and not something that will be undertaken lightly or without appropriate professional support.

Does PGD devalue affected individuals?

20. It has been suggested that the use of PND and PGD is tantamount to saying that those affected by a particular condition should not have been born, or are less valued as individuals. Another view is that there is no conflict between choosing not to have a child with a particular condition, and accepting at the same time that an affected individual should have the same rights as anyone else. To say that, if given the choice, it would be better for a child to be free of a serious disease does not necessarily reflect on attitudes towards people with that disease. However, it may be feared that an increase in genetic testing and the availability of PGD might affect people's attitudes towards disabled people and their families by creating a climate where genetic disability is increasingly seen as preventable.

21. The vast majority of people hope that their children will be healthy and free from disability. This does not mean that they will not love and care for a child born with a disability. However, the impact on the quality of life of a child born with a disability, as well as their families will depend on a number of factors. These will include the seriousness of the disability, the circumstances of the family, as well as the emotional and material support

available. Each family should be free to make their own choices in this respect and their view will be one of the most important determining factors in assessing the justification for PGD.

Why it is thought necessary to review PGD and its regulation

22. PGD has remained a relatively small-scale activity since its beginnings in the 1980s. However, there is a general growth in public awareness and interest in genetics. Genetic testing is also becoming more widely available. As public knowledge about genetics increases and more people seek tests to establish whether they are carriers of specific disorders it may be that demand for PGD will increase. It is estimated that every one of us carries approximately 1 or 2 deleterious recessive genes, but with the majority of these, problems for potential offspring only arise if both partners carry the same recessive gene. PGD may be seen as a means of selecting the physical characteristics or intelligence of children. However, this is unlikely to be a realistic possibility, partly because the technology is not yet available but also because the genetic basis of these characteristics is not properly understood. Furthermore, the HFEA and the ACGT do not think it would be acceptable to test for any social or psychological characteristics, normal physical variations, or any other conditions which are not associated with disability or a serious medical condition.

23. The HF&E Act allows for a line to be drawn permitting some activities and prohibiting others. It is the role of the HFEA to devise guidance in this respect. It has already done this in prohibiting sex selection for social reasons. This document therefore aims to consult on whether, given the potential use of PGD, there are any uses which should not be permitted or which should only be permitted under certain circumstances.

Options for families at risk of passing on a serious genetic disorder: PND and PGD compared

24. As has been mentioned, prenatal diagnosis (PND) is an option currently available to people at risk of passing on a serious genetic disorder to their children. Methods of PND include amniocentesis, chorionic villus sampling (CVS) as well as fetal blood and tissue sampling. These methods can be used to provide tissue for chromosome or DNA analysis and also for the detection of metabolic errors in the fetus. Amniocentesis and CVS carry a

small risk of miscarriage. Amniocentesis takes place relatively late in pregnancy so that where a termination is being considered this may not be possible until 18 weeks or later.

25. While PND may involve making decisions about the termination of an existing pregnancy, PGD will involve the disposal of affected embryos at their earliest stages of development. PGD therefore provides an opportunity to begin a pregnancy knowing that only unaffected embryos have been transferred. For this reason, some people may find PGD more acceptable and less traumatic. The Human Fertilisation and Embryology Act 1990 allows research on embryos up to 14 days following fertilisation. This was based on the Warnock Committee's argument that this was the earliest possible point for development of a central nervous system. For this reason PGD is likely to be more acceptable to some people than PND. However, it is acknowledged that some do not accept this distinction as they view the status of an embryo as being no different from that of the fetus.

26. Because embryos in PGD are tested at their earliest stages of development some may fear it will be too easy to test and discard them where no serious disorder exists. Currently, access to PGD is confined to individuals having a known family history of a serious genetic disorder. Furthermore, PGD cannot be considered an easy option because of the need to undergo IVF. It is therefore not a treatment that will be undertaken lightly or offer any guarantee of success. These factors appear to offer substantial practical barriers to the casual use of PGD.

27. There is already substantial professional experience and development of services with respect to the use of PND. Both PND and PGD raise the same general issues in relation to the seriousness of inherited conditions. In addition, both provide possible solutions to families who have to make difficult choices where there is a risk that their children may be affected.

28. **Do you agree with the proposal that, subject to appropriate clinical considerations, the current practice of licensing clinics to perform PGD for a limited number of specific serious inherited conditions, including sex linked disorders and chromosome abnormalities, should continue?**

Access to PGD

29. As previously mentioned, PGD is currently used by individuals at risk of having a child with a serious genetic disorder or of transmitting a chromosomal anomaly. However, there are others who may want access to PGD in the future. One potential group will be IVF patients without a known genetic risk who may wish to have the normality or viability of their embryos assessed through a process of screening for chromosomal anomalies. It is known that embryos with chromosomal abnormalities are much less likely to implant and develop, as well as being a frequent cause of miscarriage.

30. To take the possibilities one step further, the wider public may wish to have access to PGD so that embryos could be tested for a number of common disorders in circumstances where the individuals concerned are not themselves at an increased risk of passing on a genetic disorder. However, it should be stressed that there are significant problems with this approach. First of all, there is difficulty in testing individual cells for a variety of genetic conditions, and secondly, performing extra tests may have little impact on the overall risk of any genetic disorder occurring in a given pregnancy. However, the general aim would be to ensure, as far as possible, that a healthy child is born. **In due course what restrictions should there be on who might have access to PGD?**

"Seriousness" of disorder

31. Compiling a list of disorders where the use of PGD might be acceptable would necessitate defining exactly what was considered serious enough for inclusion. As knowledge about the genetic basis of certain disorders increases, the list would have to be constantly reviewed. Furthermore, individual judgements on seriousness will vary depending on personal and family circumstances and on the nature and severity of the condition and the likelihood of transmission.

32. If a couple already have an affected child or have had one or more terminations because of a genetic disorder in the fetus, they may feel less able to cope with the demands of another affected child or a further termination. In addition, they may have experience of members of their family suffering or dying from a particular disorder.

33. Furthermore, many disorders vary in the severity with which they present. Cystic fibrosis can contribute to death within a few days of birth, but some individuals may survive into their thirties and beyond. In addition, medical advances in the treatment of some genetic conditions may result in the relief of symptoms and an increased life expectancy. For example, the outlook for those with adult polycystic kidney disease has improved dramatically with dialysis and kidney transplantation. The outcome for those affected by cystic fibrosis may improve in the future with gene therapy.

34. If the HFEA does not provide a list of conditions for which PGD is permitted the decision on testing will be for the clinical team to consider with the patient. At present where the suitability of PGD is being considered, centres are understood to be applying the criteria for termination of pregnancy for fetal abnormality published by the Royal College of Obstetricians and Gynaecologists (RCOG) (Annex C). This limits the use of PND to cases where there is a precise diagnosis and a "substantial risk" of "serious handicap".

35. The HFEA and the ACGT concluded that the approach to PGD should mirror that adopted for PND and that general guidance rather than a list of specific conditions should be provided to guide clinicians on their approach to considering the use of PGD with individual patients. **Should the seriousness of a genetic condition be a matter of clinical judgement based on general guidance? If so, what aspects might such general guidance cover?**

<u>The replacement of carrier or affected embryos</u>

36. PGD will not only identify affected embryos but will also identify those that are carriers of recessive disorders. The question that arises is whether these embryos should be replaced or not. If the embryos were replaced and a child born, it would be healthy and free from the disorder but if that child's future partner was also a carrier of the same disorder there is a chance that an affected child will be born in the next generation. Carriers of particular disorders often face difficult reproductive choices and a family that has been affected by a disorder may wish to ensure that their future children will not have to experience the same difficulties. Couples may therefore choose not to replace carrier embryos as part of their treatment. The decision whether or not to replace carriers may also

be influenced by the number of embryos available for transfer. For example, following the diagnostic procedures it is possible that only carrier embryos could be available. Currently, the decision to replace carrier embryos rests with the patient in consultation with the clinical team. **Have you any comments on the general issue of replacing carrier embryos?**

37. It is also possible that in certain situations, couples may wish to replace affected embryos. This may be the intention of the couple when they first request PGD treatment, or could be the result of a situation that arises as the treatment progresses. An example that is often quoted is that of a congenitally deaf couple who feel that a child with normal hearing would be alienated from their environment and that this would be harmful to both the child and the couple. Alternatively, it is possible that in testing for one chromosome disorder another could come to light, for example Down's Syndrome. If the couple concerned felt that this was their only opportunity, they may choose to have the affected embryo replaced anyway, rather than lose the chance of having a child altogether.

38. The question therefore arises whether it is right deliberately to cause a child to be born with a disability? If a pregnant woman was found to be carrying a fetus affected by a disorder, it would not be considered appropriate to insist that she has a termination. The choice of whether to continue with the pregnancy in these circumstances would largely rest with the woman. However, in the case of PGD, because a pregnancy has not been established the nature of the choice to be made is different in that it involves a decision to begin a pregnancy knowing that a child would be born with a genetic disorder. The situation is further complicated because, by law, the clinician responsible for the treatment involving the use of PGD must consider, prior to treatment, the welfare of any child that might be born. Of course, there is no legal obligation on a woman to have any embryo implanted. **Can the principle of the welfare of the child ever be compatible with a decision to begin a pregnancy knowing that a child will be born with a genetic disorder?**

Late onset disorders

39. Many serious genetic disorders have their onset later in adult life, with the result that those affected can live normal healthy lives for years or even decades. However, some of these disorders are progressive and disabling and account for serious ill health and premature

death. Examples of late onset disorders include Huntington's disease (a serious progressive brain degeneration) and familial polyposis of the colon (an inherited form of bowel cancer). World-wide, both PND and PGD have already been carried out for these conditions.

40. However, the genes associated with some of these disorders can vary in the severity of their effect (sometimes called penetrance). Some late onset disorders follow a clear cut pattern of inheritance, where the presence of a single gene means that it is certain the disorder will eventually become evident, e.g. Huntington's. However, with other disorders, having the gene does not mean that it is inevitable that the condition will develop, only that the individual is at a very high risk. For example, having a particular mutation in a breast cancer gene may result in a 40 to 50% lifetime risk of developing breast cancer.

41. Thus late onset disorders present a dilemma. At birth a child will be healthy and free of disease, but carry the potential to develop ill health in later life. Many late onset disorders are debilitating and lead to premature death. The symptoms and prognosis may therefore be considered serious enough to justify PGD.

42. Furthermore, the word "late" is difficult to define. There are disorders which manifest themselves in infancy, e.g. Lesch-Nyhan syndrome, while there are others such as Huntington's disease, which usually has an onset later than 30 years, but with a small proportion of cases having an onset at under 15 years.

43. With conditions that do not appear at birth, but appear in later life, there will be a period where affected individuals will enjoy a "normal" life, free from the disorder. The impact of knowing that there is a certainty or strong likelihood of developing a life threatening or degenerative disease will differ from person to person and family to family. For some the cloud of the eventual illness will have a significant impact whereas others may live a comparatively "normal" life albeit of shorter than average duration.

44. Late onset disorders raise specific concerns as their effects on individuals and families can be traumatic. Therefore, one of the major factors to be considered in relation to PGD is a family's experience of living with the disorder. While the age of onset is one factor, the

seriousness of the disorder and the circumstances of the individual couple and family may be equally relevant. Furthermore, PND is already available for some of the conditions.[12]

45. **It is suggested that if a disorder is of late onset, this should be one of a number of factors, but not an overriding factor, in determining whether PGD should be offered. Do respondents consider this to be the correct approach?**

Predisposition testing

46. At some stage in the future it may be possible to test for predisposition to certain diseases where the likelihood of developing the disease is uncertain even when the gene is identified (e.g. the breast cancer gene BRCA1). The same applies to diseases where there is an interaction between environment, lifestyle and genetic predisposition. Conditions that may come into this category include some forms of Alzheimer's Disease and coronary heart disease.

47. **Should guidance distinguish between PGD for genes that are highly predictive of a serious disorder and those where the genetic component is more complex? Should the use of PGD for any indication be the subject of clinical judgement, and as such left to practitioners and individual patients to decide?**

Testing for more than one disorder

48. There may be circumstances where an individual will want more than one test carried out on their embryos. For example, an individual having PGD for one single gene defect may also be at risk from passing on another genetic defect. There may also be good reasons for carrying out a chromosome analysis. A woman over the age of 35 having PGD for a single gene defect may benefit from also having her embryos tested for Down's syndrome.

49. Another indication for multiple testing previously mentioned, is the screening of embryos for a variety of chromosomal anomalies associated with failure to implant or miscarriage. Clearly this is less to do with the prevention of genetic disease than the improvement of IVF treatment.

50. However, as genetic technologies continue to develop, it is possible that tests will be developed that screen for many genetic disorders simultaneously. If it becomes possible to detect gene defects quickly and economically, there may be requests to test all embryos created for IVF treatment to eliminate the risk of replacing those that carry one or more common serious disorders. However, as indicated previously, current technology indicates that testing for more than one genetic disorder or the use of several techniques on a single cell remains very difficult or impractical.

51. Furthermore, it would be of doubtful value to test embryos for conditions where there was no clear genetic indication in the family or medical history in the parents or other risk. The HFE Act was designed to ensure that human embryos are not used frivolously or unnecessarily, and was guided by the principle that respect is due to human life at all stages of its development. Multiple testing may not be seen as meeting this principle and, for this reason, may be considered undesirable. Furthermore, it would be possible to avoid testing embryos for a range of disorders by encouraging individuals who were sufficiently concerned about a particular disorder to be tested themselves in the first instance. This might indicate whether there was a valid indication to consider further testing on the embryo.

52. **In the context of PGD, and given the current practical limitations, should there be any restrictions on the number and range of tests to be carried out in the absence of a clear genetic or medical indication?**

Regulatory issues

53. The HFEA is responsible for licensing clinics carrying out PGD as part of IVF treatment. Subject to the responses received to this consultation, the HFEA intends to develop additional guidance for clinics to be included in its Code of Practice. In general, the HFEA's role will be to give guidance and set standards in the following areas:

- the embryo biopsy procedure;
- assessment of the laboratory based genetic tests offered;
- genetic counselling.

Embryo biopsy

54. The HFEA, with the help of specialist advice, has now drawn up training and assessment criteria for individuals carrying out the embryo biopsy part of the PGD procedure. It is intended that each biopsy practitioner will be individually inspected and assessed according to these criteria and their names registered centrally with the HFEA. The guidelines detail ways in which new practitioners can gain experience and stipulate how proficiency must be demonstrated. Detailed training records must be kept and when a potential practitioner is inspected they must demonstrate both practical abilities and extensive knowledge of the procedure. Once practitioners are licensed they will be required to submit an annual progress report to the HFEA including details of individual results and outcomes.

Laboratory tests

55. At present, each licensed PGD centre provides information to the HFEA about the safety and reliability of the tests intended for use in PGD. This is considered against an assessment of the qualifications and experience of the clinical team, the facilities and protocols to be used, the experience of the specific test in other circumstances (e.g. PND), as well as a number of quality issues, including misdiagnosis rates.

56. The HFEA inspects each licensed PGD clinic annually. It is intended that additional specialist inspectors and peer reviewers will be recruited to review applications to carry out PGD tests and also to inform licensing decisions. In the first instance, centres must demonstrate that they are competent in FISH and PCR techniques (see Annex B for an explanation of these terms). Subsequently, every new test to be used and every new disorder to be tested for must be approved by the HFEA in advance. The disorders, down to the level of each different mutation, are listed on the licence under the headings "specific diagnostic tests" and "testing for X-linked disorders". At present centres may not carry out any other tests or treat any individuals for any new disorders without the approval of the HFEA.

57. The HFEA is also exploring potential mechanisms for the accreditation of laboratories carrying out the genetic tests used in PGD.

58. **Should centres be licensed for PGD in general or in relation to each specific test and condition? Should the HFEA record each new condition, mutation or test carried out by individual centres?**

Genetic counselling

59. To ensure that individuals are informed about the reliability, accuracy, limitations and long term implications of the test that will be used on their embryos it is proposed that clinics should be encouraged to work closely with their Regional Genetic Service. Given that many patients with a family history may already be known to the Genetic Service this will help provide continuity of care and ensure that appropriate information and counselling has been provided. It is essential that individuals are well informed about the particular disorder and that they have had adequate time and opportunity to fully discuss their reproductive choices and preferred options.

a) Counselling

Genetic counselling, as part of the genetic consultation process, involves giving accurate, sensitive and complex information to the person and family in a non-directive and empathic way. The HFEA proposes that, before PGD is offered, individuals will have been through a process of genetic consultation which will have been provided by appropriately trained and experienced professionals who are part of a multidisciplinary consultant led team. It will be the responsibility of the centre offering PGD to ensure that this has taken place.

b) Information

The HFEA proposes that patient information should include references to the procedures and risks involved in undertaking IVF and embryo biopsy. This should include information about the possibility of misdiagnosis and whether it is advised that PND should be undertaken at a later stage. Reference should also be made to the experience of the clinic in carrying out the procedure in relation to specific genetic disorders.

c) Consent

Consent is an essential component of the IVF/PGD procedure. It is essential that an individual retains control over the use of their gametes and embryos and that consent to their use should only be given after sufficient information has been provided to make informed choices. The Human Fertilisation and Embryology Act 1990 (the Act) requires that consent must be given to the creation of embryos and for the purposes for which they might be used. It is proposed that individuals undergoing PGD should specify on the statutory consent form the particular diagnostic test(s) to be carried out on their embryos when giving this consent. Where testing is for an allied group of disorders, this should be made clear before consent is obtained. People should not feel under any pressure to give their consent although it is recognised that there may be external pressure from, for example, health professionals or family members to undertake testing.

d) Confidentiality

Any information about an individual relating to the provision of IVF treatment must be kept confidential under the strict confidentiality provisions of the Act. This includes any information relating to the use of a genetic test in the context of IVF. Such information may only be released to a third party with the consent of the person to whom the information relates or in an emergency where disclosure is necessary to avert an imminent danger to the health of that person.

60 **Do respondents think that the general approaches proposed for the regulation of PGD are appropriate?**

Summary

61 This document has considered the current position on PGD as well as, its likely future development and the main social, ethical and regulatory issues that arise. A number of questions have been raised and responses are sought from all interested parties. In particular, respondents are invited to answer the following questions, giving reasons where appropriate:

Paragraph 28

Do you agree with the proposal that, subject to appropriate clinical considerations, the current practice of licensing clinics to perform PGD for a limited number of specific serious inherited conditions, including sex linked disorders and chromosome abnormalities should continue?

Paragraph 30

In due course should there be restrictions on who might have access to PGD?

Paragraph 35

Should the seriousness of a genetic condition be a matter of clinical judgement based on general guidance? If so, what aspects might such general guidance cover?

Paragraph 36

Have you any comments on the general issue of replacing carrier embryos?

Paragraph 38

Can the principle of the Welfare of the Child ever be compatible with the decision to begin a pregnancy knowing that a child will be born with a genetic disorder?

Paragraph 45

It is suggested that if a disorder is of late onset, this should be one of a number of factors, but not an overriding factor, in determining whether PGD should be offered. Do respondents consider this to be the correct approach?

Paragraph 47

Should guidance distinguish between PGD for genes that are highly predictive of a serious disorder and those where the genetic component is more complex? Should the use of PGD for any indication be the subject of clinical judgement, and as such left to practitioners and individual patients to decide?

Paragraph 52

In the context of PGD, and given the current practical limitations, should there be any restrictions on the number and range of tests to be carried out in the absence of a clear genetic or medical indication?

Paragraph 58

Should centres be licensed for PGD in general or in relation to each specific test and condition? Should the HFEA record each new condition, mutation or test carried out by individual centres?

Paragraph 60

Do respondents think that the general approaches proposed for the regulation of PGD are appropriate?

References

[1] HFEA Public Consultation on Sex Selection – January 1993

[2] Handyside AH, Konotogianni EH, Hardy K, Winston RML, Pregnancies from biopsied human preimplantation embryos sexed by Y – specific DNA amplification. Nature 1990; 244: 768-170

[3] Handyside AH, Lesko JG, Tarin JJ, Winston RML, Hughes MR, Birth of a normal girl after IVF and preimplantation diagnostic testing for cystic fibrosis. N Engl J Med 1992; 327: 905-909

[4] See 2

[5] See 2

[6] Ao A, Wells D, Handyside AH, Winston RM, Delhanty JD. Preimplantation genetic diagnosis of inherited cancer: familial adenomatous polyposis coli. J Assist Reprod Genet 1998 Mar; 15(3): 140-4

[7] Harton GL, Tsipouras P, Sisson ME, Starr KM, Mahoney BS, Fugger EF, et al, Preimplantation genetic testing for Marfan Syndrome. Mol Hum Reprod 1996; 2: 713-715

[8] Conn CM, Harper JC, Winston RML and Delhanty JDA. (1998) Infertile Couples with Robertsonian Translocations: Preimplantation Genetic Analysis of Embryos Reveals Chaotic Cleavage Divisions. Hum. Genet. 102: 117-123.

[9] Delhanty, JDA, Harper, JC, Ao, A, Handyside, AH, and Winston, RML (1997) Multicolour FISH detects frequent chromosomal mosaicism and chaotic division in normal preimplantation embryos from fertile patients. Human Genetics, 99, 755-760

[10] Soussis, J, Harper, JC, Handyside, AH and Winston, RML (1996) Obstetric outcome of pregnancies resulting

from preimplantation diagnosis of inherited disease. Br. J. Obs. Gynae 103, 784-788

[11] Success rate for period 1996-7 – HFEA Seventh Annual Report 1998

[12] Advisory Committee on Genetic Testing – Genetic Testing for Late Onset Disorders

ANNEX A

Membership of the Working Group on Preimplantation Genetic Diagnosis

Professor Allan Templeton	Chairman Member of the HFEA
Ms Liz Forgan	Member of the HFEA (Until November 1998)
Professor Christine Gosden	Member of the HFEA
Dr Hilary Harris	Member of the ACGT
Professor Stuart Lewis	Member of the HFEA
Dr Anne McLaren	Member of the HFEA
Mr Philip Webb	Member of the ACGT

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TERMS OF REFERENCE

- to consider the planning, drafting, distribution and analysis of a joint HFEA and ACGT consultation document on the issues surrounding PGD; and
- to consider the practicalities of PGD licensing and the development of a licensing system.

HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY

12 November 1999

Dear Colleague

HFEA/ACGT Consultation Document on Preimplantation Genetic Diagnosis

As you will know, Preimplantation Genetic Diagnosis (PGD) has been in use since 1990, albeit on a small scale, seeking to help families to have healthy children when they are at significant risk of passing on a serious genetic disorder.

With the recent increase in understanding of the human genome and of the genetic factors involved in a range of diseases, it has become evident that there is potential for an increase in the use of PGD in clinical practice. Being aware of the public concerns in this area of medical technology, and of the social and ethical issues involved, the Human Fertilisation and Embryology Authority and the Advisory Committee on Genetic Testing established in 1998 a joint Working Group to prepare a consultation paper on Preimplantation Genetic Diagnosis.

In jointly publishing the resulting paper we are seeking to stimulate debate on whether and how PGD should be used to help such families, and to consider the ethical framework in which the technique should be regulated. The publication date for the paper is Tuesday 16 November, but I am pleased to enclose an advance copy of the document. Please note the press embargo of 00.01h on Tuesday.

This is an open, public consultation, with a closing date for comments of 31 March 2000. We are keen to encourage wide public debate on this issue, and I hope that you will find an opportunity to contribute to the discussion.

Yours faithfully

Mrs Ruth Deech
Chairman, HFEA

Rev Dr John Polkinghorne
Chairman, ACGT

Human Fertilisation & Embryology Authority
Paxton House, 30 Artillery Lane
London E1 7LS

Telephone: (020) 7377 5077
Fax (020) 7377 1871

PGD - the science

1. The first step to PGD is creating embryos outside the body by IVF. A biopsy is then carried out to remove a cell or cells from the developing embryo which can be used to test whether the embryo carries a genetic disorder. Embryo biopsy is mainly performed at the cleavage stage of embryo development, two to three days after fertilisation, when there will be 6-10 cells. Removal of 2 cells at this stage does not appear to be detrimental to subsequent embryo development[1], though continued long term monitoring of safety is required.

2. The first and/or second polar body can be removed and used to determine the genetic status of the mothers' chromosomes. The technique is currently used mainly for the detection of chromosome abnormalities, i.e. age related aneuploidy and chromosome abnormalities which are genetically inherited, such as translocations.

3. The embryo can be grown a little longer for five days to the blastocyst stage, when there is differentiation between the inner cell mass which will go towards forming the fetus and the placenta, and the outer cells which will form only placenta. At this stage a biopsy could consist of a dozen or so cells which would provide more material to work with and help improve the accuracy. However, the advantages have to be balanced against the current lack of success in growing human embryos *in-vitro* to the blastocyst stage. At present fewer than 50% of embryos will continue to develop past the cleavage stage.

4. The rate of advances in genetic technology may mean that in future less invasive methods of analysis become available and the amount of embryonic material needed for a diagnosis will be reduced.

5. The genetic diagnosis of the biopsy cells is currently attempted using one of two diagnostic techniques: fluorescent in situ hybridisation (FISH), for chromosome disorders, and polymerase chain reaction (PCR), for single gene defects. With FISH a particular chromosome is "tagged" so that it will be identifiable under a microscope when exposed to fluorescent illumination. This is most commonly used to sex embryos for patients who are at risk of transmitting an X-linked disorder (only affecting males). Tags are used for the X and Y chromosomes and only female embryos that will not develop the disorder are replaced.

6. FISH is also used to identify chromosome abnormalities for example in patients with translocation. That is where part or all of a chromosome is misplaced or missing. Tags are used for the particular chromosomes involved in the translocation so that only unaffected embryos are transferred.

7. PCR is used for the detection of genetic errors which occur at the level of the gene, e.g. single gene defects and triple repeat disorders. The DNA from a single cell is incubated with primers which bind close to the gene sequence of interest, and with the addition of an enzyme, thousands of copies are made of the relevant section of

DNA. The resulting DNA fragments can be analysed by a number of different techniques to determine whether the single cell was at risk of the genetic disease.

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[1] Hardy K, Martin KL, Leese HJ, Winston RML, Human preimplantation development in in vitro is not adversely affected by biopsy at the 8 cell stage. Hum Reprod 1990; 5: 708-714

Extract with permission from Termination of Pregnancy for Fetal Abnormality (January 1996) – Royal College of Obstetricians and Gynaecologists

Chapter 3 Interpreting the Abortion Act

3.1 The application of the Abortion Act to individual pregnancies in which the fetus is abnormal, or at risk of being abnormal, depends on the interpretation of the words that are underlined in paragraph 2.4 (see end of Annex).

3.2.1 Substantial risk

'Substantial' is not defined in the Act. According to the second edition of the Oxford Dictionary (1991) it means, amongst other things 'of real significance', 'important', 'sizeable', 'fairly large', 'real' 'having real substance'. Clearly, there is room for lawyers to argue about what risks are substantial: on the other hand a risk may be substantial without satisfying the test of being more likely than not; equally the risk must be more than a mere possibility. In the context that a decision to perform an abortion because there is a substantial risk rather than a certainty of abnormality may result in the loss of a normal fetus.

3.2.2 Many fetal abnormalities can be diagnosed with near certainty. Foe others, such as those associated with intra-uterine infection or exposure to potentiality teratogenic drugs only a probability of abnormality can be provided. Every effort should be made to obtain a positive antenatal diagnosis of fetal abnormality when this is practicable. The medical practitioners certifying that a risk is substantial should bear in mind that the risk should also be likely to be considered substantial by informed persons with no personal involvement in the pregnancy and its outcome. Factors in the decision are:

- the information that has been obtained from diagnostic procedures about the fetal abnormality;
- published studies of the outcome for such a fetus, both during pregnancy, as a child and as an adult;

3.3.1 Serious handicap

The abortion law allows the termination of pregnancy at any gestation if a fetal abnormality is untreatable and would prevent survival after birth but, if there is an abnormality that would allow long term survival, the medical practitioners have to judge whether the abnormality would be likely to result in 'serious handicap'.

3.3.2 The World Health Organisation has defined disability as follows:

"...any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being".

In interpreting the definition, the WHO considers that:

"Disability is concerned with abilities, in the form of composite activities and behaviours , that are generally accepted as essential components of everyday life. Examples include disturbances in behaving in an appropriate manner, in personal care (such as excretory control and the ability to wash and feed oneself), in the performance of other activities of daily living, and in locomotor activities (such as the ability to walk)."

The WHO has a scale of the severity of disability. Only individuals with disability at then third or higher points of the scale would be considered by most people to be seriously handicapped. Points 3 and 4 are defined as follows:

" 3. Assisted performance. Includes the need for e helping hand (ie: the individual can perform the activity or sustain the behaviour, whether augmented by aids or not, only with some assistance from another person.)
4. Dependent performance. Includes complete dependence on the presence of another person)ie: the individual can perform the activity or sustain the behaviour, but only when someone is with him most of the time)."

3.3.3 A person is only likely to be regarded as seriously handicapped if they need the support described in the WHO Points 3 or 4. However, an opinion that a particular fetal abnormality would be associated with serious handicap should be based on a careful consideration of the following factors, not all of which will be relevant in every case.

These are:

- the probability of effective treatment, either *in utero* or after birth;
- the probable degree of self-awareness and of ability to communicate with others;
- the suffering that would be experienced;
- the extent to which actions essential for health that normal individuals perform unaided would have to be provided by others;

Judgements should be cautious, recognising that it is not possible to give an authoritative view of the meaning of 'seriously handicapped' as this has not been interpreted by the courts.

3.4 **The mental health of the pregnant woman**

Women vary in their reaction to being told that their fetus is, or may be, abnormal. Occasionally a woman feels strongly that she is unable to accept a probability of risk or a degree of handicap that her medical practitioners consider less than substantial or serious. Under such circumstances, and only when the gestation is less than 24 weeks, the practitioners may decide that abortion has become necessary to protect her mental health. 'Health' has not been defined in law and it is acceptable to use the definition incorporated in the Constitution of the World Health Organisation (1946). The WHO defines health as *"... a state of physical, mental and social wellbeing and not merely an absence of disease or infirmity"*. In determining whether there is a risk to mental health in a particular pregnancy the medical practitioners have to

identify factors in the woman's life and personality that would threaten her mental health if the pregnancy were to continue: they do not have to certify that she has a mental illness. After 24 weeks the grounds for abortion for mental health are more stringent: the continuation of the pregnancy must result in grave permanent damage to mental health. Such damage to mental health is unlikely to result from a woman's concern about fetal abnormality that her doctors do not consider serious enough to satisfy the law. In effect this means that after 24 weeks the abortion decision must be based only on the anticipated risk that the child would be seriously handicapped.

Reference

Paragraph 2.4 – From chapter 2 – The Law on Abortion for Fetal Abnormality in England, Wales and Scotland

2.4 The amended Abortion Act allows two medical practitioners, acting in good faith, to certify that a pregnancy can be terminated at any gestation if *"... there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped"*. If these criteria are not met, termination after 24 weeks is permissible only if necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman or if the continuation of the pregnancy would involve risk to the *"life"* of the pregnant woman, greater than if the pregnancy were terminated. By contrast, up to 24 weeks, the Act allows a pregnancy to be terminated if *"the continuation of the pregnancy would involve risk, greater than if the pregnancy were terminated of injury to the physical or mental health of the pregnant woman or any existing children of her family."*

ANNEX D

CURRENT EXPERIENCE OF PGD (REPORT OF INTERNATIONAL CONSORTIUM)

This section provides a summary of the results from 16 European centres, covering 392 PGD cycles carried out over a period from January 1997 to September 1998. The majority of cycles were performed for age-related aneuploidy (116), and were performed by 4 centres using fluorescent in situ hybridisation (FISH, see Annex B). Forty cycles of PGD were performed for chromosome abnormalities, mainly translocations, again using multicolour FISH. Sexing was performed in 112 cycles, all for X-linked conditions. Sexing was mainly performed by FISH (104 cycles), but polymerase chain reaction (PCR) was used in 8 cycles. For cystic fibrosis, 51 cycles were performed for patients carrying various mutations, but mainly ΔF508. All the single gene defects diagnosis were performed by PCR. Thirty one cycles of myotonic dystrophy, 10 of Huntingtons chorea, and several cycles of β-thalassemia, specific diagnosis for DMD, rhesus, SMA, Marfans syndrome, Tay Sachs, adrogentical syndrome, and one cycle each of sickle cell, oesteogenesis and hypophosphateamia were performed.

From the 392 cycles started, 26 (7%) were cancelled, mainly due to a poor ovarian response to hormone stimulation. A total of 366 cycles reached oocyte retrieval. In the majority of cases, acid tyrodes was used for zona drilling to assist the biopsy (92%), but three centres used laser drilling and two used mechanical means. All centres performed the biopsy at the cleavage stage and used aspiration to remove the blastomeres (cells).

A total of 4837 cumulus complexes (in which the oocytes are located) were retrieved which is an average of 13.2 oocytes per retrieval. Of these 4473 were inseminated. Fertilisation occurred in 3046 oocytes (68%) and embryo biopsy was performed in 2395 (77% of fertilised oocytes, average of 6.5 embryos biopsied per oocyte retrieval).

The biopsy was successful in 2330 embryos (97%). 2086 embryos were successfully diagnosed (90% of those successfully biopsied, average of 5.7 embryos per oocyte retrieval), and therefore, from the oocytes collected, a diagnosis was achieved in 43%. Of those embryos diagnosed, 919 (44%) embryos were suitable for transfer, i.e. not at risk of genetic disease and 659 (32%) were transferred in 306 embryo transfer procedures. A total of 137 embryos were frozen.

Pregnancy was confirmed by observation of a positive fetal heartbeat in 67 cases, representing a pregnancy rate of 18% per oocyte retrieval, and 17% per cycle. Data on birth outcomes are still being collected, though two cases have been lost to follow up.

* The data in this section are kindly supplied by the Steering Committee of the Preimplantation Genetic Diagnosis (PGD) Consortium of the European Society for Human Reproduction and Embryology (ESHRE). A full report of the consortium data is to be published in Human Reproduction.

ANNEX E

GLOSSARY OF TERMS

Autosomal Dominant Disorders – Disorders where inheritance of a mutation from one parent only (or arising anew during egg or sperm formation) can be sufficient for the person to be affected. Important dominant disorders in the UK include familial hypercholesterolaemia, Huntington's Disease, adult polycystic kidney disease and familial adenomatous polyposis coli (colon cancer).

Autosomal Recessive Disorders – Disorders, where for a person to be affected, a mutation has to be inherited from both parents. Such parents are usually unaffected carriers because they only have a single copy of the mutant gene. Recessive disorders commonly have onset in childhood and include cystic fibrosis, sickle cell disease and thalassaemia.

Congenital malformations, deformities, diseases etc. are those which are either present at birth, or which, being transmitted direct from the parents, show themselves soon after birth.

Embryo Biopsy – Removal and examination of one or more cells from a developing embryo for diagnostic purposes.

Genetic Testing – Testing to detect the presence or absence of, or change in, a particular gene or chromosome.

Genetic Counselling – A process by which information is imparted to those affected by, or at risk of a genetic disorder. It includes information on the nature of the disorder, the size and extent of genetic risks, the options, including genetic testing, that may help clarify the risks, and the available preventative, supportive and therapeutic measures. In the context of genetic testing it may include responding to the concerns of individuals referred and their families, discussing the consequences of a test, and help to choose the optimal decision for themselves, but not determining a particular course of action.

In-Vitro Fertilisation – Sperm and eggs are collected and put together to achieve fertilisation outside the body.

Late Onset Disorder – Disorders that normally become symptomatic in adult life.

Monogenic Disorders – Disorders arising from defects in a single gene.

Multiple Birth – Birth of more than one baby from a pregnancy.

Mutation – The change in a gene or chromosome that causes a disorder or the inherited susceptibility to a disorder.

Polygenic or multifactorial conditions – The interaction of several genes and the environment.

Preimplantation Genetic Diagnosis - Use of genetic testing on a live embryo to determine the presence, absence or change in a particular gene or chromosome prior to implantation of the embryo in the uterus of a woman.

Prenatal Diagnosis

(a) Amniocentesis – This method involves examining fetal cells taken between 15 and 16 weeks of pregnancy from the amniotic fluid which surrounds the fetus. The fetal cells are cultured and the genetic make-up of the fetus determined. This allows testing for chromosomal abnormalities such as Down's syndrome and other birth defects.

(b) Chorionic Villus Sampling (CVS) – This method involves the removal of a small sample of placental tissue between 9 and 11 weeks of pregnancy which is tested for genetic abnormalities.

Triplet or trinucleatide repeat disorders – caused by the expansion of a triplet repeat of bases within a gene and are usually associated with neurological disorders e.g fragile X, Huntington disease, myotonic dystrophy. Each disease has a range of repeats associated with a spectrum from normal to affected individuals.

X-Linked Disorders – Disorders due to a mutation on the X chromosome. X-linked disorders usually only affect males, but the disorders can be transmitted through healthy female carriers.