

## **Preimplantation Genetic Diagnosis (PGD) – Guiding Principles for Commissioners of NHS services**

### **1. Summary**

Preimplantation genetic diagnosis (PGD) is an extension of prenatal diagnosis, using IVF technology to enable couples at high risk of passing a serious genetic disorder to their offspring to avoid an affected pregnancy. It is a relatively new and developing technique that has some clinical utility within a range of options for reproductive choice (and for some couples it may be the best option). However evidence of effectiveness and safety is limited and success rates (in terms of take home babies) are not high. On current evidence PGD may be a good use of resources in some individual cases after careful counselling and assessment but should not be regarded as a standard service.

This paper provides an overview of PGD. It sets out possible indications for PGD, examines the alternatives and briefly reviews the supporting evidence. The regulatory framework is outlined and comparative information presented on some aspects of current service provision. The paper does not aim to be a detailed service review but does highlight a wide variation in levels of activity between the units offering PGD. It reflects discussions from a workshop held in June 2002 for representatives of all UK units licensed to provide PGD services and commissioners of NHS services.

The Genetics Commissioning Advisory Group (GenCAG) has considered the issues, has accepted that there is a limited role for PGD and recommends that individual cases could be considered by commissioners for NHS funding. A set of guiding principles has been endorsed by GenCAG to aid commissioners in making these assessments (see section 10).

### **2. Definition of PGD**

Preimplantation Genetic Diagnosis (PGD) uses in vitro fertilisation (IVF) to create embryos, tests one or two cells from each embryo for the specific genetic abnormality and identifies unaffected embryos for transfer to the uterus. The approach through PGD assists couples at risk of an inherited disorder to avoid the birth of an affected child. The range of genetically transmissible conditions for which testing is possible is continually increasing and examples licensed by the Human Fertilisation and Embryology Authority for PGD include fragile X, muscular dystrophy, Huntington's disease.

### 3. Indications for PGD

The reasons for requesting PGD include:

- Patients with chromosomal disorders
- Couple at risk of transmitting serious genetic disorders to their offspring

The possible clinical indications for PGD will widen. The Human Fertilisation and Embryology Authority has just allowed concomitant HLA typing so that the resulting child will be free of the family's genetic condition and be a compatible donor of cord blood stem cells to help treat an affected sibling. Two centres have suggested that PGD should be offered as a screening procedure to couples undergoing IVF for infertility<sup>i</sup> <sup>ii</sup> and another suggests that PGD could have a role as part of the diagnostic work-up for all couples experiencing recurrent miscarriage.<sup>iii</sup> This so-called aneuploidy screening (checking for certain abnormalities of chromosome number) may increase the pregnancy rate for infertile couples undergoing IVF but there is no good evidence that it increases the chance of a live birth. The use of these techniques as part of IVF for infertility should be considered distinct from PGD for couples at high risk of genetic disorders.

### 4. Alternatives to PGD

Families known to be at risk of transmitting genetic disorders to their children have other options apart from PGD. These are:

- To decide not to have a child
- To conceive naturally and have prenatal diagnosis (PND) during the pregnancy (involving the invasive procedures of amniocentesis or chorion villus sampling). If the fetus is found to be affected the parents then have to decide whether to opt for termination of pregnancy (with the provisions of current legislation)
- To have a pregnancy without prenatal testing, taking the decision to live with the risks and consequences of an affected child (which might include recurrent miscarriages of non-viable fetuses)
- To adopt a child
- To consider assisted conception techniques in which one or both partners would not be the biological parent of the child.

### 5. Evidence of efficacy

A recent review of the literature concluded that the literature on effectiveness of PGD was limited to case series and one under-powered and poorly controlled trial. Reliable evidence could not be identified to compare effects of PGD with other pre-natal diagnostic strategies on take home baby rates, abortion rates for diagnosed abnormalities or congenital abnormalities. There was limited evidence from case series that missed diagnosis is rare using PGD, but nothing on actual sensitivity of the technique for detecting chromosomal or genetic abnormalities. There was little in the literature to clarify the efficacy, safety and accuracy of PGD in couples undergoing IVF.<sup>iv</sup>

The latest published data from the European Society of Human Reproduction and Embryology (ESHRE) PGD consortium was not included in the review. This includes information cumulated by 26 collaborating centres between 1994 and May 2000 on 886 couples, 1318 PGD cycles, 163 pregnancies and 162 live-born babies.<sup>v</sup> Around 30% were for chromosomal abnormalities (e.g. translocations and aneuploidy risk), 25% X-linked conditions (e.g. Duchenne/Becker's muscular dystrophy, Fragile X syndrome, haemophilia) 25% autosomal recessive conditions (eg cystic fibrosis, thalassaemia, spinal muscular atrophy) and around 20% autosomal dominant conditions (eg myotonic dystrophy, Huntington's disease). Success rates for clinical pregnancy were quoted as 16.5% per started cycle, 18% per oocyte retrieval and 22% per embryo transfer procedure. Half the resulting pregnancies underwent prenatal diagnosis. Of these, there were four cases of misdiagnosis. Information on malformations was available for 130 of the children; 121 had no abnormality, 7 had non-life threatening malformations and 2 had lethal malformations. ESHRE data to May 2001 gave slightly improved outcomes for the most recent year, with a pregnancy rate of 19% per oocyte retrieval and 23% per embryo retrieval (compared with 17.3% per oocyte retrieval and 22% per embryo transfer for cumulative data over three years).<sup>vi</sup>

There is little known from the literature about the acceptability of PGD to couples, nor the likely demand for the technique. A recent study of a small number of PGD patients found that over 75% of couples contemplating a future pregnancy would chose to undergo PGD again.<sup>vii</sup> A recent review in the Journal of Medical Genetics concluded that, after a decade of practical application PGD remained 'a technically challenging, multistep, labour intensive procedure which requires the close collaboration of a team of specialists.'<sup>viii</sup>

## 6. Regulation of PGD

Under the Human Fertilisation and Embryology Act 1990 treatments involving in vitro fertilisation must be carried out in licensed centres. The Human Fertilisation and Embryology Authority considers it essential that clinical embryo biopsy (necessary for PGD) is carried out within a standard IVF setting against a background of clinical protocols within a licensed centre.

The Authority has issued interim licensing guidance for PGD and plans to review the guidance in the light of comments received following consultation on the document prepared by a joint working group between the HFEA and the Human Genetics Commission (formerly Advisory Committee on Genetic Testing). Centres carrying out PGD may only apply the procedure in the disorders specifically listed in their licence, but may apply to the HFEA for further licences:

- to test for a genetic disorder not already licensed for that centre
- to use a new probe for a disorder already licensed for a particular probe(s)

- to test for different mutations of a disorder for which that centre already has a licence
- to carry out tests for new chromosome aberrations

In considering a licence application the HFEA requires information on:

- Staff involved (embryo biopsy practitioners require an HFEA license)
- Procedures for obtaining consent and consent forms
- Clinical and laboratory protocols
- Arrangements for genetic counselling
- Decision-making process to determine whether PGD should be offered
- Patient information:
  - Reference to the process, procedures and risks involved in undertaking IVF and embryo biopsy procedures in the context of the provision of a sophisticated genetic test.
  - Reference to the experience of the clinic in carrying out the procedure.
- Information about the efficiency and reliability of probes used for the laboratory diagnosis:
  - the centre's knowledge of the use of the probe in the context of PND;
  - the centre's experience of the use of any tissues and controls they have used in order to develop the probes;
  - the centre's experience of the human embryo and controls they have used in order to develop the probes;
  - whether the person carrying out the procedure carries out a test on other cells of the embryo to confirm a positive test and details of false positive results;
  - whether there are any checks in pregnancy and how the centre informs and advises patients of these
  - the centres views on communicating misdiagnosis rates to subsequent patients
- Information on disorder
  - The known risk
  - Severity of the particular case
  - The way it affects the family
  - The mode of inheritance

## 7. Availability of PGD

The HFEA currently licenses 6 centres in the UK for PGD:

- Glasgow
- Guy's / St Thomas'
- Hammersmith
- Leeds General Infirmary
- University College Hospital, London
- Care at the Park Hospital, Nottingham

The Nottingham centre is a private hospital – NHS treatment takes place at the other centres on the list. PGD has been offered to patients at the Hammersmith since 1990 (although research commenced in the 1980s), at UCH since 1996 and Guy's/St Thomas' since 1997. The Leeds service was

granted a licence in 1997 but has not been able to offer its service consistently. The Glasgow centre has only recently received its licence and is yet to undertake treatment cycles.

## 8. Current provision

**Table 1 - Information on NHS services**

	UCH	Hammersmith	Leeds	Guy's / St Thomas'
Conditions tested - Single gene defects (number) - Fetal sex - Chromosome disorders	10 Yes Translocations, insertions, inversion and T21 mosaicism	6 Yes Translocations, Turner's, T21 mosaic	1 Yes	6 Yes Rearrangements, including translocations, insertions, inversions etc
Source of referral - Clinical genetic - Self (overseas) - GP - Other specialty	60% 20% 10% 10%	50% Yes Yes 25% (assisted conception)		70% less than 5% less than 5% 20% (assisted conception)
Number of referrals - Total - Accepted - Refused	Years 1997-2001 274 210 (77%) 64 (23%)	Years 1987-2001 81	Years 1997-2001 89	Years 1997-2001 617
Source of referrals	London & SE 46% Midlands 10% N. England 16% SW 5% Scotland 4% N. Ireland 4% Wales <1% Overseas 14%	Private and NHS	Yorkshire region Northern region NW Wales	London & SE Midlands SW Wales North England N. & S. Ireland Other (not specified – none from overseas)
Cost: Consultation and investigations IVF cycle Genetic diagnosis	£680 £2550 - £3250 £1500-£2250	£3605 per cycle (including all treatment, drugs and tests)		£3,000 per cycle (includes all consultations, IVF/ICSI treatment, tests and genetic diagnosis – excludes drugs)

**Table 2 - Activity and outcome data**  
(all data as numbers unless specified)

	UCH 2000 - 2001	Hammersmith 1987-2001	Leeds 1997-2001	Guy's / St Thomas 1997-2001
Patients treated	19	81		90
IVF cycles	26	160	14	150 (128 egg retrievals)
Cycles completed to embryo transfer		119		96
Affected embryos	129			527
Unaffected embryos	66			252
Pregnancies	6 (2 ongoing)	27		34 (6 ongoing)
Babies born	5 (includes twins)		2 (1 misdiagnosis)	31 (7 twins, 2 triplets, 1 affected)
Clinical pregnancy per couple		33%		33%
Live birth rate per couple		25%		28%

## 9. Should PGD be a part of NHS provision?

A number of factors need to be taken into account when considering whether PGD is reasonable use of limited NHS resources. Table 3 sets out some of the advantages and disadvantages of PGD to help inform debate. There have been discussions over whether any funding for PGD should be part of genetics budget or infertility services budgets. Anecdotally, commissioning authorities have applied their often tight eligibility criteria for IVF to couples requesting PGD although circumstances are different and these individuals may already have living children, albeit affected with a genetic condition, and may be older than the defined age limits for NHS-funded IVF. Table 4 sets out the similarities and differences between PGD and IVF for infertility to help inform decisions over whether IVF criteria should apply to PGD patients or not.

**Table 3 Advantages and disadvantages of PGD**

Advantages	Disadvantages
Widens reproductive choice, especially as an alternative to prenatal diagnosis where termination of pregnancy unacceptable	Low success rate (in terms of take home babies)
Can provide a better approach to PND for certain genetic disorders where there is uncertainty over the magnitude of risk and disease outcome for offspring	Prenatal diagnosis recommended to avoid the birth of an affected child (and for other genetic disorders in current screening programmes)
Empowers couples at risk of transmitting serious genetic disorder to offspring to take a positive approach to reproduction	Emotionally and physically draining (may not be acceptable)
May avoid need for repeat terminations of pregnancy	Uncertainty over longterm effects of procedure on offspring
May reduce repeat miscarriages	Gaps in current evidence base – Technology Outcomes Acceptability Health economic assessment
May prevent birth of child with serious genetic disorder	

**Table 4 A comparison of IVF for infertility patients and PGD**

Similarities between IVF for infertility and PGD	Distinctions between IVF for infertility and PGD
Common goal – healthy baby	A type of prenatal genetic diagnosis
Possibility of psychological harm as unable to reproduce normally	Previous experience of offspring / pregnancies affected by serious genetic disorder
Techniques in common	Overt costs to NHS of couples at risk of transmitting genetic disorder: - repeat PND +/- TOP - repeat miscarriages - birth of affected children

## 10. Guiding Principles to aid funding decisions for PGD

Following discussion at the Genetics Commissioning Advisory Group and at a workshop for commissioners and providers of PGD services, the following guiding principles were agreed and are recommended to commissioners as an aid to assessing requests for funding PGD cycles for individual couples.

1. PGD may be a legitimate approach to reproductive choice in certain individual circumstances, given the current state of knowledge and practice.
2. The HFEA maintains a regulatory function over PGD that includes consideration of quality of service provision and issues licences for individual procedures and diseases in accordance with its criteria – commissioners should look to the HFEA to continue to define which diseases are licensed for PGD.
3. Each case requesting funding for PGD should be considered individually.
4. Priority should be given where the risk of offspring affected by the disorder is greater than 10%.
5. IVF for infertility policies usually have strict criteria restricting access for older women and people with living children. These criteria may be inappropriate in the case of those PGD patients who have a long history of unsuccessful outcomes in pregnancies or who have living children affected by a serious genetic disorder.
6. Consideration should be given to the family structure, with greater priority given to people with no living or no healthy children.
7. A limit to the number of cycles funded would be appropriate – the first cycle for a couple is the most costly as it includes genetic testing and the development of the specific diagnostic probe and a further 1-2 cycles for that couple would increase the chance of a pregnancy and make the best use of genetic probe development.
8. Requirements for the PGD service should be agreed with commissioners, to include:
  - Referral pathways to PGD services (see below), to include at what point in the pathway the funding request is to be forwarded to commissioners in PCTs.
  - Adequate opportunities for couples to undergo genetic counselling to discuss and understand all possible options before they have progressed too far down the pathway.
  - Clear links between PGD services and other health care professions, including primary care and referring clinicians.
  - HFEA licence, which implies conformity of service delivery with HFEA standards and guidance.

- Participation in internal and external collaborative audit, to include audit of effectiveness and outcome and contribution of data to consortia such as the European Society of Human Reproduction and Embryology.

## **11. Pathway for PGD**

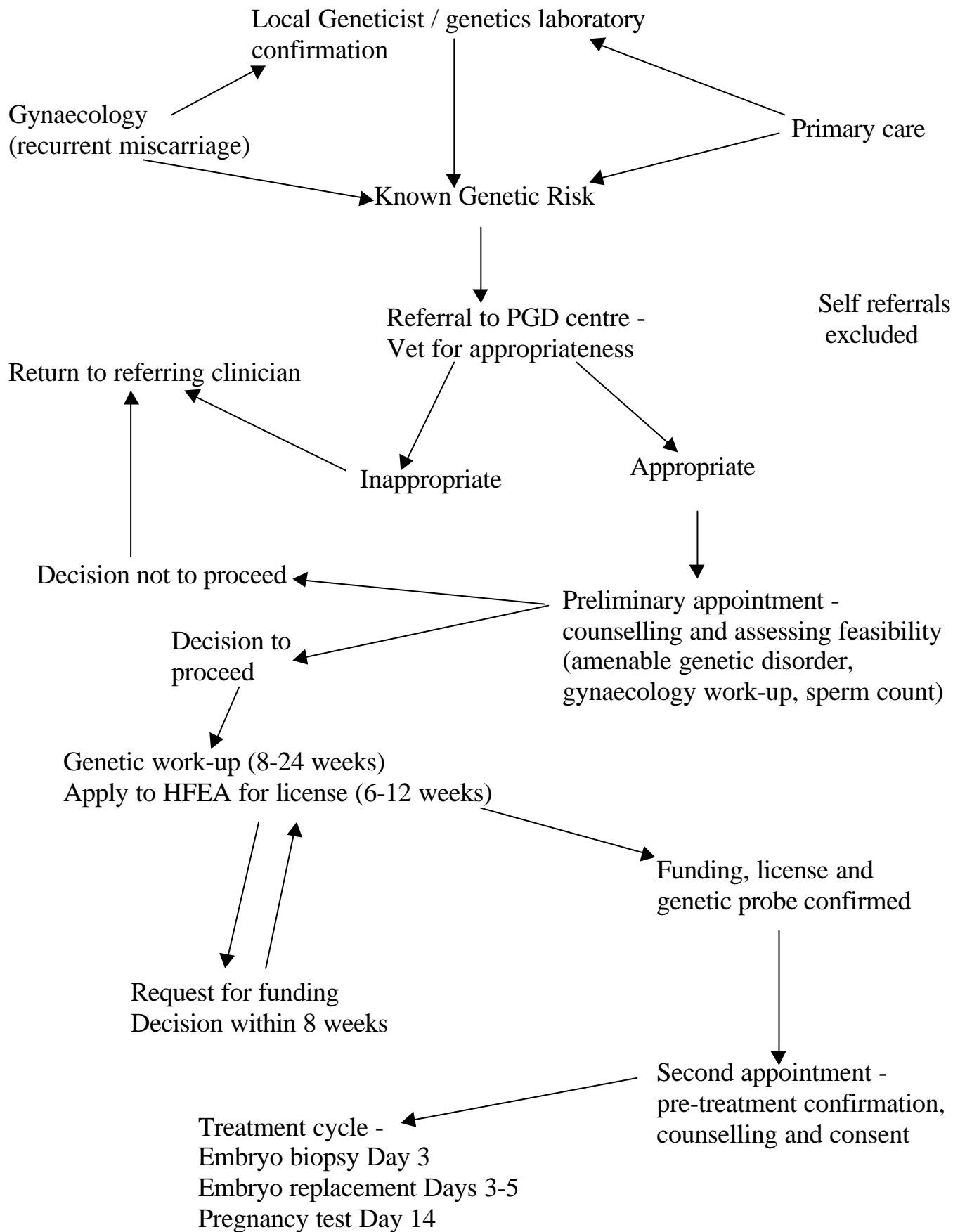
Participants at the June 2002 workshop on PGD agreed that a consistent and streamlined pathway for referral, assessment and funding decisions would be beneficial to patients, service providers and commissioners. It was recognised that funding would not be available to all couples requesting PGD but that equity would be improved if common principles and processes were applied to referral and assessment of NHS patients. The pathway in annex A identifies critical decision points and reinforces the point that couples need good information at a preliminary discussion to allow them to make an informed decision whether or not to proceed (as a significant number will decline when they understand what PGD involves).

## **12. Information for commissioners**

On submitting a request for funding, adequate information should be provided to enable commissioners to carry out a timely assessment. This information should include the following:

- Type of genetic condition and risks to offspring
- Date of birth of female
- Relevant family history – including previous children to either partner and whether or not affected
- Relevant reproductive history – and why PGD the most appropriate option
- Route of referral to the PGD centre
- Chances of a successful outcome
- Fee package – and what the fee covers
- Likely timing for treatment
- GP (of female)
- Postcode

It was agreed that the most helpful presentation of fees was as a package for the pathway. This could include counselling, diagnostic work-up, drugs, IVF procedures and embryo biopsy and genetic testing. Second and subsequent cycles may be at a discounted rate as they might not include the additional cost of probe development (although some centres have one package price for all cycles which includes only a proportion of the probe development costs).



**Annex A**  
**Referral Pathway for PGD**

## References

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- <sup>v</sup> ESHRE PGD Consortium Steering Committee. Data collection II (May 2000). European Society of Human Reproduction and Embryology 2000;15(12):2673-83.
- <sup>vi</sup> ESHRE Preimplantation Genetic Diagnosis Consortium: data collection III (May 2001). Human Reproduction 2002;17(1):233-246.
- <sup>vii</sup> Lavery SA, Aurell R, Turner C, Castellu C, Veiga A, Barri PN, Winston RM. Preimplantation genetic diagnosis: patients' experiences and attitudes. Human Reproduction May 2002;17:2464-7.
- <sup>viii</sup> Kanavakis E, Traeger-Synodinos J. Preimplantation genetic diagnosis in clinical practice. J Med Genet 2002;39:6-11.