

Legal aspects of PGD Licensing

Regulation of PGD

1. The HFE Act does not specifically mention the use of PGD; however as the prohibitions in the act state that the creation, use or storage of embryos cannot be performed without a licence from the HFEA, there is no doubt that it is covered by the Act. The Warnock Report described the use of an embryo biopsy for detecting abnormalities before implantation as a possibly useful technique, but came to the conclusion that it was unlikely to be used for some time.
2. The Act states that the embryos must be in a suitable condition to be placed into a woman¹ and the activity must appear to the Authority to be "*necessary or desirable for the purposes of providing treatment services*"² for a treatment licence to be granted.

Licences

3. PGD applications are considered by a licence committee. Recently a fast track licensing process has been introduced, this aims to reduce the burden of regulation on centres. Practically it means that if a condition has already been licensed at another clinic, the issue is not considered again by a licence committee.
4. In licensing a susceptibility gene condition, a further consideration arises, in that different mutations in a specific gene can cause different effects. This is very noticeable in the BRCA gene where the position of the mutation within gene can give rise to either ovarian or breast cancer. It is also possible that different mutations within the same gene (or mutations in different genes) can cause variable penetrance. For example one mutation could cause a 50% penetrance whereas a different mutation could result in a 90% penetrance for the same condition.
5. Licensing individual mutations within a gene would be complicated and contrary to the new fast-track licensing process, however some consideration needs to be made about the variable nature of susceptibility gene conditions if an application were received.

The Code of Practice

¹ HFE Act 1990 Schedule 2 1(1)

² HFE Act 1990 Schedule 2 1(3)

6. The HFEA Code of Practice states that PGD is only available to patients if there is a “*significant risk of a serious genetic condition being present in the embryo*”³ and significant risk is not defined.
7. The Code of Practice sets out the factors which should be taken into account when PGD is offered:
 - (i) *The view of the people seeking treatment of the condition to be avoided*
 - (ii) *Their previous reproductive experience*
 - (iii) *The likely degree of suffering associated with the condition*
 - (iv) *The availability of effective therapy, now and in the future*
 - (v) *The speed of degeneration in progressive disorders*
 - (vi) *The extent of any intellectual impairment*
 - (vii) *The extent of social support available*
 - (viii) *The family circumstances of the people seeking treatment*

Prenatal diagnosis and the law

8. Prenatal (PND) is usually undertaken in weeks 10-24 of a pregnancy and can be used to determine if a fetus has inherited a specific genetic condition. PND is governed by the Abortion Act 1967, as amended by the HFE Act 1990.⁴ Section 37(1) (d) states that abortion is legally permitted if two medical practitioners are agreed that “*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.*”⁵ If abnormalities are discovered using PND, it is this clause which can be used to perform terminations if required. Less than 1% of abortions performed in the UK are under this section of the act.
9. There is no definition of “handicapped” in English law, however it has been defined by the World Health Organisation as ‘a disadvantage for a given individual resulting from an impairment or a disability that limits or prevents the fulfilment of a role that is normal for that individual’. The lack of definition of what constitutes a serious handicap, allows a broad definition within the Act.

House of Lords decision regarding the HFEA and PGD licensing

10. The Hashmi case was an important case to test the powers of the

³ Code of Practice 14.22

⁴ HFE Act 1990 37(1) (d)

⁵ The abortion Act 1967 1(1)(d)

HFEA to licence PGD in different circumstances. Although the Act and the House of Lords decision do not give an idea of what the limits are, it does suggest that the HFEA has power to licence PGD including for HLA alone. Therefore, this suggests certain scope to allow PGD for conditions where a *child* is not affected by a condition (but in the case of a susceptibility gene the adult *may* be).

PGD in other countries

11. PGD is offered by many different countries, but is generally only practiced by a few centres in each country. The regulation differs from country to country, ranging from a complete lack of legislation or guidelines to countries in which any use of embryos is illegal. More details of PGD in other countries can be found in the table below.

PGD regulation in other countries, and conditions for which PGD is available.

Country	PGD Law/Guidelines	Examples of conditions used for
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Australia –
Victoria

The Infertility Treatment Act 1995
PGD is permitted in Victoria where a doctor specialising in human genetics is satisfied that a genetic abnormality or a disease might be transmitted as a result of the pregnancy. There is no definition within the act of a genetic abnormality or a disease which might be serious enough or significantly affect the health of a person to permit PGD. The act has deliberate ambiguities to allow for a broad interpretation

The Act states four guiding principles when offering fertility treatments; the welfare and interest of the person born or to be born are paramount, human life should be preserved and protected, the interests of the family should be considered, and infertile couples should be assisted in fulfilling their desire to have children. It is the intention of the act to use PGD to prevent the passing of conditions or abnormalities which will significantly affect the health of the person to be born.

The decision to offer PGD must be made by an appropriately qualified medical doctor, with all the expertise available to him/her. Once a centre has been licensed to perform a specific test they do not need to apply again for that condition. Any new applications will be submitted to the authority, who will then pass it on to an ethical committee if they feel it needs ethical approval (see table for examples of where case by case assessment is needed)

Conditions already licensed for:

- recurrent implantation failure
- recurrent miscarriage
- advanced maternal age
- previous history of foetal aneuploidy
- known carriers of chromosomal rearrangements

Determination of sex in cases of :

- Becker's Muscular Dystrophy
- Duchenne's Muscular Dystrophy
- Haemophilia
- Kennedy Disease

Heritable single gene disorders:

- 35delG Mutation in Connexin-26 Gene
- Adrenoleukodystrophy
- Alagille Syndrome
- Alpha-1-antitrypsin
- Alpha-Thalassaemia
- AZF-c Deletion of the Y Chromosome
- Beta Thalassaemia
- Becker's Muscular Dystrophy
- BRACA1 Mutation
- Cystic Fibrosis
- Duchenne's Muscular Dystrophy
- Fragile X
- FAPP
- Hereditary Sensory Neuropathy Type 1
- Huntingdon's Disease
- Kennedy's Disease
- Lesch Nyhan Syndrome
- RhD Factor Incompatibility
- Spinal Muscular Atrophy
- Tuberous Sclerosis

Examples of PGD which require approval on a case by

cases basis:

- Autosomal recessive conditions where it is proposed to

• HLA with PGD ⁶		
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⁶ Infertility Treatment Authority, Victoria, Australia – www.ita.org.au

Belgium There are only 4 centres doing PGD, there is no central board to make decisions about conditions that are permitted, the decision is taken locally by institutional review boards.

Centre for Medical Genetics, Dutch-Speaking Brussels Free University

Monogenic diseases:

- Achondroplasia (G380R G>A)
- Adrenogenital syndrome (A656G)
- Autosomal dominant polycystic kidney disease
- Carbohydrate Deficient Glycoprotein syndrome type 1A (intragenic polymorphism)
- Charcot-Marie-Tooth disease type 1A (linked markers)
- Cystic fibrosis (all mutations)
- Deafness
- Duchenne's muscular dystrophy (linked markers)
- Fragile X syndrome (triplet repeat)
- Haemophilia A (duplex markers)
- Huntington's disease (CTG repeat)
- Huntington's disease exclusion
- Incontinentia pigmenti
- IVS1+5 G>C in conjunction with HLA typing
- Kennedy disease (CGG repeat)
- Marfan syndrome (mutation specific and linked markers)
- MCAD deficiency
- Myotonic dystrophy (CTG repeat)
- Neurofibromatosis type 1 (mutation specific and linked markers)
- Neurofibromatosis type 2 (mutation specific and linked markers)
- Other single gene defects (custom)
- Retinoblastoma (duplex markers)
- Sickle cell anemia (+HLA typing)
- Spinal muscular atrophy
- Spinocerebellar ataxia types 1 and 7
- X-linked agammaglobulinemia (duplex markers)

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- X-linked Alport syndrome (duplex markers)
- Beta-thalassemia

● Embryo sexing for X linked disorders 7		
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⁷ List of Indications ESHRE www.eshre.com access date 17/05/05

France	<p>Article L. 2131-4 (CSP) of law 94-654 dated July 29, 1994, et Decree n° 98-216 of March 24, 1998 states that biological diagnosis based on cells sampled from an embryo in vitro is only permitted in exceptional circumstances for example:</p> <ul style="list-style-type: none"> ● A physician practising in a pluridisciplinary prenatal diagnosis centre as defined by article L.2131-1, must certify that the couple, because of their family background, has a strong possibility of giving birth to a child affected by a particularly severe genetic disorder, recognised as incurable at the time of diagnosis. ● Diagnosis can only be made if the anomaly or anomalies causing such a disorder have been previously and specifically identified in one of the parents. ● Both members of the couple must express in writing their consent to the diagnostic procedure. ● The diagnosis can have no other purpose but to detect this disorder and seek the means of preventing or treating it. ● The diagnosis may only be performed under certain conditions, in an institution specifically licensed to do so with the approval of the National Committee for Reproductive and Prenatal Diagnosis Medicine and Biology. 	<p>Used, but only 3 centres, Strasbourg, Montpellier and Strasbourg:</p> <p><i>Monogenic diseases:</i></p> <ul style="list-style-type: none"> ● Achondroplasia ● Cystic fibrosis (all mutations) ● Familial adenomatous polyposis (most mutations) ● Fragile X syndrome ● Huntington's disease ● Huntington's disease/exclusion test ● Myotonic dystrophy/Steinert ● Spinal Muscular Atrophy ● Tay-Sachs disease ● Von Hippel-Lindau syndrome (all mutations) ● Beta-thalassemia (all mutations in exon 1 and 2) / sickle cell anemia <p><i>Chromosome abnormalities:</i></p> <ul style="list-style-type: none"> ● Chromosome translocations ● Embryo sexing for X linked disorders⁸
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⁸ List of Indications ESHRE www.eshre.com access date 17/05/05

<p>Germany</p>	<p>Law for the protection of embryos 1990 There are two relevant articles:</p> <ul style="list-style-type: none"> ● <u>Article 2-1</u> punishes anyone using a human embryo for any other reason than ensuring its survival. ● <u>Article 8-1</u> defines the embryo as a fertilised human ovum capable of development as soon as fusion of the nuclei has taken place. According to this article, every totipotent cell harvested from an embryo is also an embryo which must be protected. <p>PGD would be classified as detrimental to the embryo and therefore illegal, however this has been avoided by using first and second polar bodies so screen.</p>	<p>Aneuploidy screening and maternal translocations by first and second polar bodies</p>
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⁹ Article 12 of the Convention is concerned with predictive genetic tests, and states that: "Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling."

The Netherlands	<p>Each case reviewed on a case by case basis, must be approved by CCMO (Centrale Commissie Menselijk Onderzoek.) Usually it is only permitted for condition which PND is available for.</p> <p>The Netherlands are a signatory to the Oviedo Convention.⁹</p>	<p>Academic Hospital Maastricht Dept of IVF:</p> <p><i>Monogenic diseases:</i></p> <ul style="list-style-type: none"> • Cystic fibrosis • Familial Adenomatous polyposis coli (FAP) • Fanconi anaemia • Fragile X syndrome (linkage analysis, CGG repeat) • Huntington's disease • Leigh syndrome (T9176C mutation - mitochondrial disease) • Marfan syndrome (linkage analysis) • Myotonic Dystrophy / Steinert • NARP/Leigh syndrome • Spinal Muscular Atrophy (SMA) • Spino Cerebellaire Ataxie (SCA) type 3 • Tuberous Sclerosis type 1 • Tyrosine hydroxylase defeciciency <p><i>Chromosome abnormalities:</i></p> <ul style="list-style-type: none"> • Chromosome deletions • Chromosome inversions • Chromosome translocations • Embryo sexing for X linked disorders <p>ERASMUS MC Rotterdam:</p> <ul style="list-style-type: none"> • Aneuploidy screening¹⁰
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¹⁰ List of Indications ESHRE www.eshre.com access date 17/05/05

<p>USA</p>	<p>There are no federal laws in the USA directly concerning the use of PGD, the FDA has limited control, but over the quality of the equipment used rather than the process itself.</p> <p>Professional body guidance: the ASRM (American Society of Reproductive Medicine) provides guidance to all who practice PGD and related activities, it is a clinical not an experimental procedure and so is not subject to Institutional Review Boards. The ASRM also have an ethics committee who also publish guidance.</p> <p>Litigation as a method of PGD regulation (tort) – plaintiff must prove that the clinician owed a duty of care, which was breached and this resulted in injury.¹¹</p>	
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¹¹ Published in 2004 The President's Council on Bioethics, Washington. Reproduction and responsibility: the regulation of new biotechnologies. <http://www.bioethics.gov/reports/reproductionandresponsibility/chapter3.html>