Preimplantation genetic diagnosis

German Ethics Council

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HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY

Human Fertilisation and Embryology Act 1990 (as amended)

Schedule 2

Para 1ZA (1) A licence … cannot authorise the testing of an embryo, except for one or more of the following purposes -

(a) establishing whether the embryo has a gene, chromosome or mitochondrial abnormality that may affect its capacity to result in a live birth [PGS]

(b) in a case where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality,

(c) in a case where there is a particular risk that any resulting child will have or develop -

(i) a gender-related serious physical or mental disability,

(ii) a gender-related serious illness, or

(iii) any other gender-related serious medical condition,

establishing the sex of the embryo

Human Fertilisation and Embryology Act 1990 (as amended)

Schedule 2

1ZA (2) A licence under paragraph 1 cannot authorise the testing of embryos for the purpose mentioned in sub-paragraph (1)(b) **unless the Authority is satisfied—**

(a) in relation to the abnormality of which there is a particular risk, and

(b) in relation to any other abnormality for which testing is to be authorised under sub-paragraph (1)(b), that there is **a significant risk that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition**

No longer case-by-case decision-making:

Centres wishing to carry out embryo testing must apply to the HFEA for a licence:

- Must have suitable facilities and equipment.
- Must have competent staff and validated processes.
- Must have appropriate patient information and consent forms.
- Must have access to a multi-disciplinary team.

No longer case-by-case decision-making:

- Once a centre has been licensed to carry out PGD, it can do so for any of the conditions listed on the website:
  http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm
- If a centre wishes to carry out PGD for a condition which is *not* on the list, it must apply to the HFEA.
- A centre must notify the HFEA the first time it carries out PGD for one of the conditions on the list.
- If a centre is authorised to carry out PGS, it can do so for all chromosomes.

Application to HFEA for a licence:

- Does not have to be ‘family specific’ (as it did pre-2009).
- But usually centres *do* have a specific family in mind.
- Must provide evidence that there is a significant risk of serious abnormality.
- A lay summary of the condition will be published on the HFEA website to allow any interested parties to comment on the application. These comments will be reviewed by the Licence Committee assessing the application.

Conditions waiting consideration are published on HFEA website. Currently:

Genetic condition	OMIM1
Sanjad Sakati syndrome	4141011/08/2010
Ataxia telangiectasia	20890011/09/2010
Alpha mannosidosis	24850016/09/2010
Autosomal Recessive Severe Combined Immunodeficiency with bilateral sensorineural Deafness	26750028/10/2010
Methylmalonic aciduria and homocystinuria	27740015/11/2010
Autosomal Dominant Hyper IgE Syndrome	14706023/11/2010
Mucolipidosis type II	25250001/12/2010

Application process II:

- Application will be sent to peer reviewers (clinical geneticists).
- The views of patient groups may be sought.
- The decision on whether embryo testing should be allowed for the particular disease/condition will be determined by the Authority's Licence Committee.
- If approved, the condition will be published on the HFEA website and all PGD centres will be notified of its approval by email.
- All PGD centres will then be able to offer PGD for the newly approved condition.

Application process III

- The HFEA will review all conditions / diseases on the central list every five years for their suitability for PGD.
- 'Living' list: conditions can be removed (perhaps if effective treatment becomes available) as well as added.
- There are some conditions/tests which still have to be licensed on a case by case basis:
  - late on-set, lower penetrance disorders (eg BRCA1/2)
  - preimplantation tissue typing.

Licence Committee's 'Explanatory Note'

When considering the significance of the risk, the Licence Committee will take into account the penetrance of the condition:

The options are:

- full penetrance (100% - i.e. it is a certainty that a person with the abnormality will develop the condition in question) or

- incomplete penetrance, which is usually presented as a range of percentages (e.g. 40 – 60%) I.e. only a subset of people with the abnormality will develop the condition

Licence Committee's 'Explanatory Note'

When assessing the seriousness of the disability, illness or condition, the Licence Committee will take into account the following factors:

(a) Age of onset.

Is the condition congenital or does it manifest later in life? If it does manifest later, at what stage (childhood, early adulthood, later)?

(b) Symptoms of the disease.

What are the symptoms of the condition?

Is the condition potentially fatal, life threatening or life limiting?

(c) Whether the condition is treatable

Licence Committee's 'Explanatory Note'

(d) What type of treatment is available for those conditions that can be treated

What is the extent of the treatment available? How invasive is the treatment or likely treatment?

(e) Effect of the condition on quality of life

This will include any evidence about the speed of degeneration in progressive disorders and the extent of any physical and /or intellectual impairment.

Licence Committee's 'Explanatory Note'

(f) Variability of symptoms

Symptoms associated with the same condition can vary from family to family (and from individual to individual), and can range from the mild to the severe.

Where the condition has variable symptoms, the Licence Committee will take account of:

- what the range of variability is; and
- whether the range suggests that some forms of the condition are so mild that they might not meet the 'serious' test.

Licence Committee's 'Explanatory Note'

When deciding whether to licence the condition (not the particular family's circumstances):

- Where a condition has a range of penetrance (e.g. 40-60%), the Licence Committee will base its decision on the highest penetrance figure.
- Where a condition has variable symptoms, the Licence Committee will base its determination of how serious the disability, illness or condition is, on the worst possible symptoms.

Even if a condition is on the list, the Centre must follow the Code of Practice

Para 10.6 The centre should consider the following factors when deciding if PGD is appropriate in particular cases:

a) the views of the people seeking treatment in relation to the condition to be avoided, including their previous reproductive experience

b) the likely degree of suffering associated with the condition

c) the availability of effective therapy, now and in the future

d) the speed of degeneration in progressive disorders

e) the extent of any intellectual impairment

f) the social support available, and

g) the family circumstances of the people seeking treatment.

PGD statistics

- HFEA receives, on average, two applications for new PGD conditions per month.
- In 2008, 182 patients underwent 214 PGD treatment cycles. This represents 0.42% of all IVF cycles.
- There were 54 live births resulting in 66 babies. This represents 0.44% of all IVF babies.
- The live birth rate (births per cycles started) was 25.2%.

PGS: a controversial technique

Licence Condition T89 … before the people seeking treatment give consent to preimplantation screening of embryos for aneuploidy they must be given an oral explanation supported by relevant written material:

ii. of the unproven nature of the procedure, in particular that more robust clinical and laboratory trials are needed to assess whether or not PGS can significantly increase live birth rates for different specific indicators and it is likely that the method of fluorescent in situ hybridisation (FISH) on embryos, using a limited number of chromosomes, is not effective at increasing live birth rates…

v. that the more chromosome tests that are used, the higher the technical failure rate, and the lower the chance of finding suitable embryos for transfer

Morphological analysis

- All centres carry out visual morphological analysis.
- Licence condition T91:

  Centres may use non-invasive procedures, for example metabolomics, to test and select for the viability of embryos. However, centres must not use these procedures to test for specific gene, chromosome or mitochondrion abnormality without prior authorisation from the Authority.

Counselling

- All patients receiving IVF, including PGD, must be offered counselling
- Code of Practice provides that patients receiving PGD must have access to a genetic counsellor.
- HFEA does not collect statistics on the uptake of counselling.

Controversy?

- Human Fertilisation and Embryology Act 2008 amended 1990 Act to put embryo testing on statutory footing.
- 1990 Act silent on PGD, so rules were developed in HFEA Code of Practice.
- Statute adopted the pre-2008 HFEA criterion ‘substantial risk of serious condition’

Lord Darzi
Hansard 19 Nov 2007 Column 666

The Bill will impose a **statutory ban on the sex selection of offspring for non-medical reasons**. This will put on the face of the legislation something which is at present a matter of HFEA policy, giving Parliament the opportunity to fully debate the provisions. **The Bill will also make explicit the basic parameters for screening and selecting embryos**. Again, the intention is that this should be undertaken only on the grounds of avoiding serious disease.

Recent trends in PGD:

- Greater public awareness, greater interest in PGD.
- PGD patients are (usually) not infertile. HFEA and clinics have tended to focus on the treatment of infertility. Need to accommodate different types of patient.
- PGD is expensive. It is sometimes available within the NHS.
- Prenatal testing and abortion is much cheaper.

Variability of seriousness *within* conditions

For genetic conditions which have multiple types, approving the overall condition might result in the Authority approving a form of the condition that does not meet the statutory tests.

As a result, for some conditions, only certain variations are licensed.

- Niemann-Pick Type A (OMIM #257200) – this accumulation occurs very quickly, an affected child will usually die before reaching three years of age.
- Niemann-Pick Type B (OMIM #607616) – does not affect the brain and, although growth may be slow, those affected will survive into adulthood, with many being able to lead a full and normal life.

So - approve Type A but not Type B.

But what if variation is known but not yet understood?

Publication of data:

- In September 2009, the Authority agreed to publish a complete list of all licensed PGD conditions, along with the OMIM number of each licensed condition.
- If centres believe that there are particular 'exceptional circumstances' where there is a heightened risk of patient identification for a particular reason, they must provide evidence supporting this assertion along with their application.
- The Chair and Chief Executive of the Authority will then decide on the basis of this evidence and evidence from peer reviewers whether or not to withhold publication of the condition / disease from the central list.

Future trends:

- Declining use of sex selection to avoid sex-specific conditions. Testing for the condition enables more embryos to be available for transfer.
- Once a condition is on the ‘list’, clinics must decide whether it meets the seriousness criterion in the particular couple.
- HLA-typing and late onset conditions, review case by case decision-making?