

# Embryo testing: Testing for more than one condition at a time

<b>Strategic delivery</b>	<input checked="" type="checkbox"/> Setting standards	<input checked="" type="checkbox"/> Increasing and informing choice	<input type="checkbox"/> Demonstrating efficiency economy and value
<b>Details</b>			
Meeting	Authority		
Agenda item	9		
Paper number	HFEA (20/01/2016) 783		
Meeting date	20 January 2016		
Author	Anjeli Kara, Regulatory Policy Manager		
<b>Output</b>			
For information or decision?	For decision		
Recommendation	To decide on one of the policy options set out in this paper, while considering balancing patient choice with the handling and interpretation of genetic information		
Resource implications	HFEA policy staff resources		
Implementation date	01 April 2016 (Update to Code of Practice)		
Communication(s)	Both internal and external communications on possible changes to guidance on embryo testing in the Code of Practice		
Organisational risk	<input type="checkbox"/> Low	<input checked="" type="checkbox"/> Medium	<input type="checkbox"/> High
Annexes	Annex A: Proposed amendments to guidance note 9: PGS Annex B: Proposed amendments to guidance note 10: Embryo testing		

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## 1. Background

- 1.1.** Over the years, embryo testing technologies have developed to enable practitioners to carry out the same tests with more speed and accuracy. The latest technologies, however, can also test for more than one genetic condition or abnormality at a time. This development, brought with technologies called karyomapping and next generation sequencing (NGS), has implications for how we regulate embryo testing and how clinics handle the additional genetic information generated.
- 1.2.** The Scientific and Clinical Advances Advisory Committee (SCAAC) has been watching the development of these technologies over the past few years, and referred the issues to the Ethics and Standards Committee (ESC) for consideration of the legal and ethical implications in 2014. We discussed the issues with stakeholders at an embryo testing workshop in December 2014, and through correspondence with a number of professional bodies and a genetic charity. The stakeholder views gathered support the use of these technologies in practice and the concept of testing for more than one disease at a time. These findings were presented to the [Authority in May 2015](#).
- 1.3.** The Authority expressed misgivings about the type of patients currently being offered preimplantation genetic screening (PGS)<sup>1</sup> by clinics and how complex test results could be interpreted. It was therefore agreed that these comments should be further considered before a decision is made. This paper addresses the Authority's comments before asking for a decision on whether it is appropriate to test for more than one condition or abnormality at a time. The Authority's choice will come down to where it wishes to strike the balance between maximising patient choice and being concerned about the implications of handling and interpreting additional genetic information.
- 1.4.** The options for regulating embryo testing technologies and handling the complex information generated as a result are set out in this paper. Before considering them, we provide background on the latest technologies; outline SCAAC's most recent discussions on PGS (including revised guidance for consideration); and consider how complex test results could be managed and interpreted in clinical practice.

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## 2. What are the latest embryo testing technologies?

- 2.1.** There are two main types of embryo testing: preimplantation genetic diagnosis (PGD)<sup>2</sup> and PGS<sup>1</sup>. Technologies used in PGD identify embryos that are at risk of being affected by an inherited genetic or chromosomal condition by looking for irregularities

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<sup>1</sup> Preimplantation genetic screening (PGS) identifies embryos carrying an abnormal number of any of the 23 pairs of chromosomes. Embryos that are shown to carry a common chromosomal abnormality are not transferred.

<sup>2</sup> Preimplantation genetic diagnosis (PGD) identifies embryos carrying a specific genetic mutation or chromosomal translocation that is known to exist in the patient couple's family history. Embryos that are affected by the condition being tested for are not transferred and therefore do not result in a child being born. Embryos that are carriers and non-carriers for the condition can be transferred.

in DNA (ie, mutations) or by looking at chromosomal translocations<sup>3</sup>. PGS screens embryos for common chromosomal abnormalities (eg, an increase or decrease in the number of chromosomes) that can cause miscarriage or IVF failure. There are therefore two ways embryos can be tested: by chromosome analysis<sup>4</sup> (PGS and PGD for chromosomal translocations) and detecting mutations in DNA (PGD for genetic conditions).

### Next generation sequencing

- 2.2.** Next generation sequencing (NGS) – the latest technology in chromosome analysis – involves fragmenting the DNA in a cell from an embryo and checking parts of chromosomes (rather than analysing chromosomes as a whole which all previous technologies allowed). This offers increased accuracy, higher resolution, and lower diagnostic costs. For these reasons NGS is becoming the ‘go-to’ technology for detecting chromosomal abnormalities, and allows PGS and PGD for chromosomal translocations to be carried out at the same time. NGS is also widely used across the NHS in genetic testing laboratories.

### Karyomapping

- 2.3.** Like other technologies for detecting genetic conditions, karyomapping works by tracing the gene for a serious condition in affected prospective parents or family members, and comparing it to the genetic material of their embryo(s) to see if it carries the same mutation – this is known as haplotyping. Due to the higher resolution it provides and the shorter time it takes to generate results, karyomapping is becoming the ‘gold standard’ in targeted haplotyping and for detecting genetic mutations, and can also carry out PGD for multiple genetic conditions at once (as long as a reference sample is available for all conditions being tested for).
- 2.4.** While karyomapping is primarily used for detecting genetic conditions, it can also be used for complete chromosome analysis. Therefore, when used alongside a reference sample, karyomapping enables PGD and PGS to be carried out at the same time (ie, more than one genetic condition or chromosomal abnormality can be tested for at a time).
- 2.5.** It is not possible – as technology currently stands – to test an embryo for an assortment of conditions from an embryo biopsy sample alone, as a reference sample from a relative with a condition would not exist. It is worth noting, however, that advances in genetic testing could make it possible for embryo testing to be carried out without the need for a reference sample, and for whole genome sequencing technologies to become widely available in the future.

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<sup>3</sup> Chromosomal translocations occur when DNA from one chromosome is swapped with DNA on another chromosome. If there is no gain or loss of DNA, it is called a balanced translocation.

<sup>4</sup> Chromosome analysis involves looking at the number of chromosomes present in a cell and/or identifying whether parts between chromosomes, which are not from the same person, have been rearranged.

### Incidental findings

- 2.6.** Incidental findings are genetic findings that are unintentionally discovered when testing an embryo with the latest technologies. These findings are unrelated to the medical condition for which testing has been sought and cannot always be interpreted. This means an incidental finding that cannot currently be interpreted may, or may not, have a clinical effect on a child born.
- 2.7.** The latest embryo testing technologies can highlight incidental findings. Incidental findings from NGS may include gains or losses of parts of chromosomes, and mosaicism<sup>5</sup> in embryos. Incidental findings from karyomapping can include genome-wide chromosome malsegregation (which can indicate abnormal fertilisation and other early abnormal events in the embryo) and gains or losses of parts of chromosomes. This means that when PGD is carried out to test for specific conditions, incidental findings about chromosomal abnormalities may be revealed. Conversely, when PGS is carried out to test for chromosomal abnormalities, the test may also reveal information about certain conditions linked to chromosomal abnormalities or information about other chromosomal problems.

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## 3. Embryo testing technologies and the law

- 3.1.** PGS and PGD is regulated by the Human Fertilisation and Embryology Act 1990 (as amended) (the Act) in different ways.

### Preimplantation genetic screening

- 3.2.** A patient may have their embryos screened for a range of chromosomal abnormalities which might be causing repeated IVF failure or miscarriages, if the following criterion in the Act is met:

Schedule 2, 1ZA(1)(a): 'establishing whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth.'

- 3.3.** There is no specific authorisation process in place for the use of PGS in individual cases; centres which are licensed for embryo testing validate the use of PGS for each category of patients to which it is offered.

### Preimplantation genetic diagnosis

- 3.4.** PGD can be carried out by a centre with an embryo testing licence, providing patients meet the criterion laid out in the Act:

Schedule 2, 1ZA(1)(b): 'in a case where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality,

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<sup>5</sup> Mosaicism is the phenomenon where cells from the same person/embryo have two or more populations of cells with different genetic makeup.

establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality.’

- 3.5.** In practice, this means that PGD for inherited genetic and chromosomal conditions can be carried out where there is an existing known risk of a genetic disease in a family (ie, meets the ‘particular risk’ requirement). Once this risk has been established, PGD can be offered to patients with a family history of a serious inherited condition, providing the HFEA has agreed that the disease in question is sufficiently serious (ie, known as ‘significant risk’) and is included on the [list of authorised PGD conditions](#).
- 3.6.** Although the use of PGS and PGD in clinical practice are well established, use of the latest embryo testing technologies gives rise to two new scenarios:
- Patients may wish to have both PGS and PGD at the same time.
  - Patients may wish to use PGD to test for more than one genetic condition at a time.

#### Carrying out PGS and PGD at the same time

- 3.7.** We sought legal advice about whether PGS and PGD can be carried out at the same time. The advice concluded that embryo testing for PGS and PGD should be considered separately and the requirements for each must be satisfied before testing is carried out. The Act requires that embryo testing cannot be carried out unless ‘one or more’ of the purposes set out are met. This means that if a patient satisfies the requirements for PGS, it does not act as a gateway to carrying out PGD. Likewise, if a patient satisfies the requirements for PGD, this does not mean that the patient is automatically eligible for PGS. However, if a patient satisfies the requirements for both PGD and PGS, both forms of embryo testing can be carried out at the same time.

#### Carrying out PGD for more than one genetic condition

- 3.8.** We already know that it is possible for a couple who are unlucky enough to have a family history of two diseases to test their embryos for both conditions – provided both diseases are on the Authority’s list of authorised PGD conditions. This is because they fulfil the particular risk requirement for both conditions. However, whether it would be possible to test for more than one disease when the couple has a particular risk of just one condition required clarification.
- 3.9.** The legal advice indicates that it would be possible for an embryo that has satisfied the particular and significant risk requirements for PGD for one genetic condition, to also be tested for additional conditions at the same time, provided they satisfy the significant risk test. There is no need for the additional genetic conditions to meet the particular risk requirement too.

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## 4. SCAAC’s recommendations on PGS

- 4.1.** In line with the Authority’s recommendation in May 2015, SCAAC considered the Code of Practice guidance note on PGS at their June meeting, and made the following recommendations:

- Based on the current level of evidence, the Authority should not recommend PGS for particular patient groups (and patient information on the HFEA website should reflect this).
- Guidance around information provision for patients should be updated to reflect the use of the latest embryo testing technologies.
- Genetic information generated through embryo testing technologies should be interpreted by experts in genetics and embryo testing.
- Patients should be offered access to both genetic and infertility counsellors, and given guidance on questions they should ask.
- Patients should be given information explaining the misdiagnosis rate associated with PGS for aneuploidy.

**4.2.** In light of the Committee's comments, proposed amendments to the PGS guidance note are set out at Annex A of this paper. Amendments to the patient information are currently underway and will go live with the launch of the new website.

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## **5. Handling, interpreting and sharing the complex data generated through the latest embryo testing technologies**

- 5.1.** Beyond the legal considerations, we need to think about how centres and their patients should deal with the information generated from the latest embryo testing technologies. How should information be shared between professionals, patients and their wider families, and what should be done with information that cannot currently be interpreted? Further, what kinds of consent do patients need to give and what kind of counselling support should they be able to access?
- 5.2.** Following the Authority's discussion on this topic in May 2015, we have considered how other organisations that have needed to address similar questions have approached this area (eg, Genomics England). We have also considered best practice guidelines issued jointly by the Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics, and by the Association of Clinical Genetic Science. These guidelines address consent and confidentiality in clinical genetic practice<sup>6</sup>, and targeted NGS<sup>7</sup>, respectively. Both guidelines have been taken into account in the recommendations below, and should be referenced when providing guidance to the sector.
- 5.3.** Before considering how all of the relevant information gathered would come together in a typical patient experience of undergoing PGS and PGD using the latest technologies,

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<sup>6</sup> Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics. Consent and confidentiality in clinical genetic practice: Guidance on genetic testing and sharing genetic information (A report of the Joint Committee on Medical Genetics): [www.bsgm.org.uk/media/678746/consent\\_and\\_confidentiality\\_2011.pdf](http://www.bsgm.org.uk/media/678746/consent_and_confidentiality_2011.pdf)

<sup>7</sup> Association for Clinical Genetic Science. Practice guidelines for targeted next generation sequencing analysis and interpretation: [www.acgs.uk.com/media/774807/bpg\\_for\\_targeted\\_next\\_generation\\_sequencing\\_may\\_2014\\_final.pdf](http://www.acgs.uk.com/media/774807/bpg_for_targeted_next_generation_sequencing_may_2014_final.pdf)

the following sections summarise the sector and stakeholder opinions gathered to date, and highlight the key points of the best practice professional guidelines.

### Rights to information generated by embryo testing technologies

- 5.4.** The storing of genetic information raises confidentiality issues for patient(s) undergoing treatment and any potential consent taken during the consultation process. This is a complex area, and obtaining and retaining genetic information about any individual engages Article 8 of the European Convention of Human Rights. Article 8(1) states that everyone has the right to respect their own private and family life, although this privacy needs to be balanced against the rights and freedom of others. The right not to know is recognised in Article 10.2 of the Convention on Human Rights and Biomedicine, which notes that everyone is entitled to know any information collected about their health; however, the wish to not be informed should also be observed.
- 5.5.** In the context of genetic testing, there can be wider familial implications as a patient may not wish to receive certain information about their genetic status, such as information which indicates that they may suffer from a disorder for which there is no cure. The Authority already recognises this and provides guidance in the Code of Practice for managing PGD for non-disclosure<sup>8</sup>.
- 5.6.** Stakeholders largely agreed that many patients would want access to any information generated through embryo testing, however ambiguous the findings may be. They felt that patients should see an expert in interpreting genetic data and discuss their options in the light of the information generated. This thought is echoed in professional guidance on sharing genetic information<sup>6</sup>.

### 'Blocking out'

- 5.7.** Some stakeholders thought that genetic information which cannot help select an optimal embryo for transfer should not be tested for. For this to happen in clinical practice, areas of array-based technologies would be 'blocked out' to avoid testing for conditions that are not on the Authority's list of authorised PGD conditions. However, blocking out would only be possible with array-based technologies, would not be adaptable to all the latest embryo testing technologies (eg, karyomapping), and could exclude future technologies.
- 5.8.** If blocking out is carried out in practice, in accordance with external legal advice, the Authority would need to be satisfied that it is to prevent the embryo from being tested for abnormalities, rather than preventing the dissemination of information about such a test.

### Interpreting information generated by embryo testing technologies

- 5.12.** As noted above, the latest technologies in embryo testing can generate incidental findings. It is current practice for diagnostic laboratories to flag these findings to centres and state, where necessary, whether they are able to determine the effect an

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<sup>8</sup> PGD for non-disclosure is where patients at risk of a late onset disease wish to use PGD to avoid the condition without discovering whether or not they themselves will develop the disease later in life

anomaly may have on a child born. Therefore, the decision currently lies with the clinician on which embryo to transfer in accordance with HFEA guidance.

- 5.13.** For this particular reason, stakeholders have flagged the importance of obtaining patient consent and offering access to both genetic and infertility counsellors. This would enable patients to make informed choices about their treatment and the handling of genetic information that may be gathered, and would provide them with emotional support both before and after testing has occurred. Reports generated by diagnostic laboratories that highlight incidental findings to centres (as outlined above), was considered fit for purpose by stakeholders.

#### Counselling and recording consent for embryo testing technologies

- 5.14.** Due to the complexity of embryo testing and the factors involved, it is widely considered by stakeholders, the sector and professional guidelines that patients – including affected family members that provide reference samples – should be given access to both genetic and infertility counsellors<sup>9</sup>, before and after testing. This is so patients fully understand how the technologies work, the information technologies might reveal – both positive and negative – the information they want to receive, and are given sufficient time and emotional support to consider the implications.
- 5.15.** It was widely felt that consent should be recorded and tailored to the type of embryo testing taking place, and note patient wishes around the disclosure of information. This is reflected in professional guidance on sharing genetic information<sup>6</sup> and practised by the 100,000 genomes project which uses the latest genetic testing technologies.

#### Future genetic testing technologies

- 5.16.** It is important to acknowledge that genetic testing is a rapidly evolving field. Non-invasive prenatal testing is a sophisticated blood test that examines the DNA of a fetus in the maternal bloodstream, to determine whether it is at risk of a common chromosomal abnormality. Although this technique does not fall under the remit of the Authority, it is important to note this advance in technology, what it allows, and that it is becoming more available in clinical practice.
- 5.17.** Regarding embryo testing in particular, both the sector and stakeholders flagged that the Authority should consider the likelihood that advances in genetic testing will eventually make it possible for embryo testing to be carried out without the need for a reference sample from an affected relative. Further, if whole genome sequencing becomes more widely available – rather than a specialist test for paying members of the public as is currently the case – this could result in an increased number of PGD cycles (eg, a member of the public could find that they/a relative has a condition after having their genome sequenced and could seek PGD treatment as a result).

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<sup>9</sup> Genetic counsellors have factual information on the risks, incidences and implications of genetic disorders. Infertility counsellors provide patients with emotional support and time to consider implications.

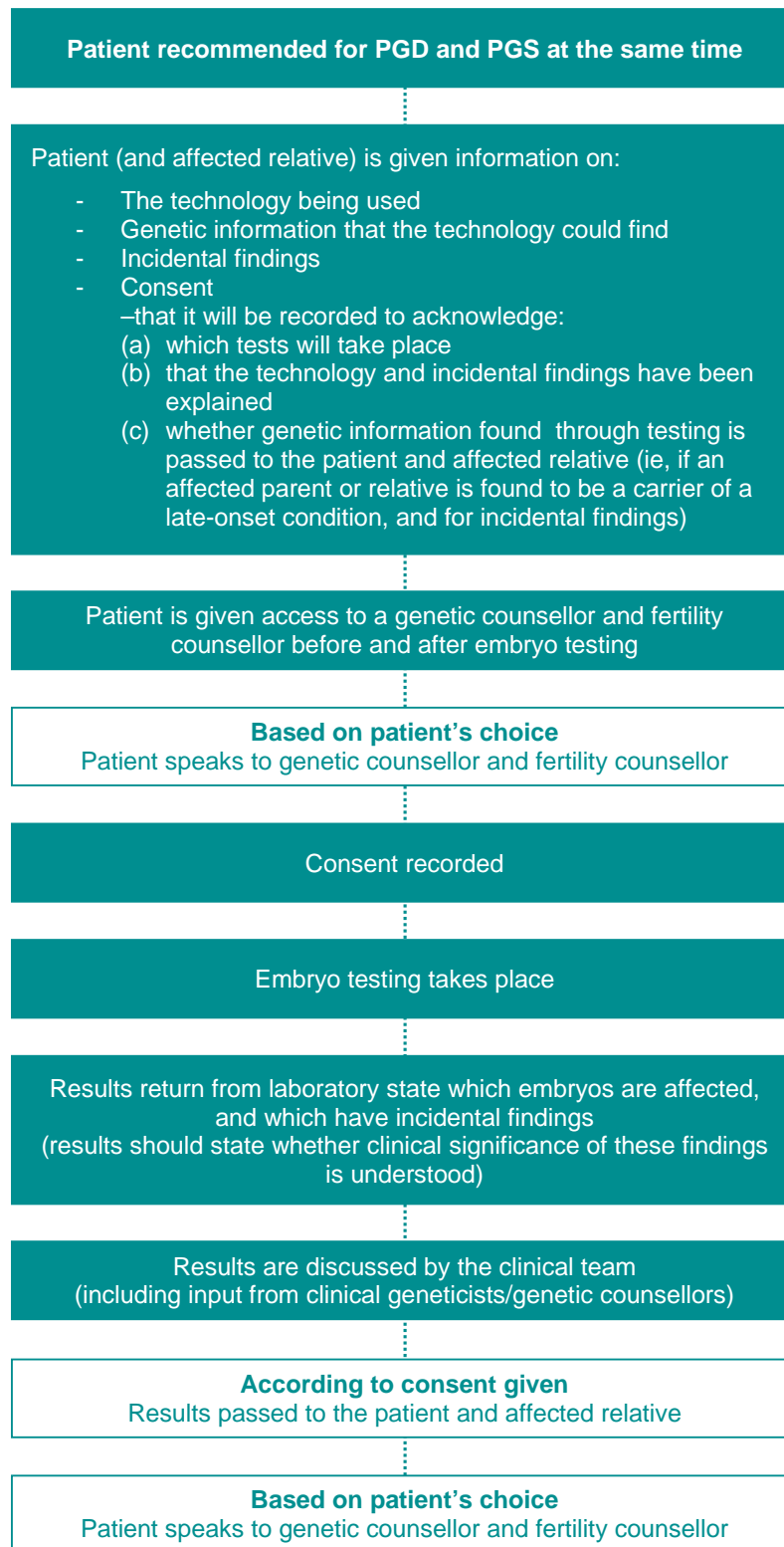


### Patient pathways

- 5.18.** Taking the abovementioned information into consideration, Figure 1 shows an overview of how this information would come together for a patient experience undergoing PGD and PGS.

It is worth noting that unlike PGD, there is currently no specific authorisation process in place or particular patient group requirements for the use of PGS in individual cases – this will remain unchanged. However, given the scenarios that the latest embryo testing technologies allow, it is anticipated that there will be additional information, counselling and consent requirements for clinics to meet when treating patients undergoing PGS (eg, access to a genetic counsellor, obtaining consent for non-disclosure of incidental findings, where necessary).

- 5.19.** Taking on board this patient experience pathway, Annex D details how the Code of Practice guidance note on embryo testing could be amended.



**Figure 1:** Summary pathway of patient undergoing PGS and PGD at the same time

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## 6. Policy options

**6.1.** How should the HFEA regulate embryo testing in light of the latest technologies? The legal advice is clear that:

- PGS and PGD can both be carried out for the same patient, provided that they meet the criteria for both types of embryo test.

This means it is possible to test for a chromosomal abnormality and a genetic condition at the same time – indeed this is happening in some clinics.

- PGD can be used to test for more than one genetic condition at a time, providing the ‘particular risk’ requirement is met for at least one condition and the ‘significant risk’ requirement is met for all conditions.

This means that two or more genetic conditions could be tested for on the same embryo at the same time. This is happening in clinical practice where a patient meets the ‘particular risk’ requirement for both conditions (ie, when a patient has more than one inherited disease in their family).

**6.2.** An important starting point would be the provision of information and genetic counselling to the patient(s) prior to embryo testing as part of the consent process. This would provide the opportunity for the wishes of patients to be obtained and recorded, and a basis for a clinic to act if an abnormality concerned (or perhaps an incidental finding) is identified.

**6.3.** Stakeholders have suggested that regardless of the type of embryo testing that is carried out, patients must:

- give appropriate consent
- be given sufficient information about the procedure (including the technology used); and
- be given access to a genetic counsellor and/or a clinical geneticist.

Consent and information provision should be specific to the type of testing carried out and there should be a relevant expert available to help patients understand the information generated by the test.

### Testing for more than one genetic condition and/or chromosomal abnormality at a time

**6.4.** As outlined above, the legal advice is clear that the Act allows for PGS and PGD to be carried out at the same time, and PGD to be used to test for more than one condition at a time. However, it is appropriate to allow this? The Authority is asked to decide one of the following possible policy options.

- Option 1: To prohibit testing for more than one genetic condition or chromosomal abnormality at a time
- Option 2: To allow testing of more than one genetic condition or chromosomal abnormality at a time, making sure that patients consent to receive (or not receive) the information generated

Option 1	Option 2
<p>Prevents patients undergoing PGD and PGS at the same time; and prevents PGD for more than one disease at a time where the patient only meets the 'particular risk' requirement for one condition.</p> <p>This option would only involve using some of the latest technologies (as blocking is not possible for all).</p>	<p>PGS and PGD can be carried out for the same patient, provided that they meet the criteria for both types of embryo test; and PGD can be used to test for more than one genetic condition at a time, providing the 'particular risk' requirement is met for at least one condition.</p> <p>SCAAC's recommendations on PGS are included in the next Code of Practice update.</p>
<b>Benefits</b>	
<p>Ensures only genetic conditions for which patients' meet the particular risk requirement are tested for.</p>	<p>Patients can make an informed decision about whether they would like to receive any additional genetic information about their embryos, which may increase their chance of a live birth and/or healthy child.</p>
<p>Patients are not faced with receiving incidental findings/genetic information about their embryos, for which the clinical significance is unknown.</p>	<p>Patients are able to give consent confirming their wishes, and are offered both genetic and infertility counselling to help make informed decisions.</p>
	<p>Allows embryo testing using the latest technologies and sets a provision for future advances in the area (eg, consent and genetic counselling).</p>
	<p>Reflects the expert opinions gathered from the sector, stakeholder organisations, professional guidelines and genetic charities.</p>
<b>Risks</b>	
<p>Patients are not informed decision about any chromosomal abnormalities or incidental findings that could affect a child born.</p>	<p>Depending on the number of conditions and abnormalities tested for, this may lead to a reduction in the number of unaffected embryos to transfer.</p>
<p>Blocking is only available on certain embryo testing technologies and not all.</p>	<p>Testing may reveal conditions that have implications on the wider family (eg, late onset conditions).</p>
<p>Does not allow embryo testing using all of the latest technologies and it could prevent the use of future technological advances.</p>	<p>Testing may give rise to incidental findings and genetics expertise may not be available to interpret complex test results.</p>
	<p>Not recommending PGS for a particular patient group may lead to an increase in PGS cycles for patients that may not see a benefit.</p>
	<p>May increase the cost of a treatment cycle.</p>

**Table 1:** Benefits and risks associated with both policy options.

- 6.5.** Note: In May 2015, three policy options were presented to the Authority, however, one option – to allow testing of more than one genetic condition, but withhold from patients the information that is generated – was considered an inappropriate approach.

**Recommendation to the Authority**

- 6.6.** The Authority is asked to consider both options and decide on the appropriate approach. The Authority's choice will come down to a decision about where it wishes to strike the balance between maximising patient choice and being concerned about the implications of handling and interpreting additional genetic information.
- 6.7.** Depending on the approach taken, the Authority is asked to approve the proposed amended guidance to the sector on 'PGS' (for Option 1 and 2) and 'embryo testing' (for Option 2, only) as set out at Annex A and B of this paper, respectively. These changes will be incorporated in the April 2016 update of the Code of Practice.

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## Annex A: Proposed amendments to guidance note 9: Preimplantation genetic screening (PGS)

### Mandatory requirements

Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

#### *Schedule 2*

#### *Licences for treatment*

- 1 (1) A licence under this paragraph may authorise any of the following in the course of providing treatment services—
- ...
- (b) procuring, keeping, testing, processing or distributing embryos...

#### *Embryo testing*

- 1ZA (1) A licence under paragraph 1 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 mitochondrion abnormality that may affect its capacity to result in a live birth,
- (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,

#### Licence conditions

- T88 With respect to any embryo testing programme involving biopsy the centre must ensure that:
- a. no embryo is transferred to a woman where that embryo or any material removed from it or from the gametes that produced it, has been subject to a test that supplies genetic information about the embryo, unless the test has been expressly authorised by the Authority, and
- b. any information derived from tests on an embryo, or any material removed from it or from the gametes that produced it, is not used to select embryos of a particular sex for social reasons.
- T89 With respect to any embryo testing programme the centre must ensure that embryo testing is only being carried out for those genetic conditions that are expressly authorised by the Authority.

#### HFEA Guidance

Staff to be involved in PGS

- 9.1** The centre should ensure that a multidisciplinary team is involved in providing the embryo testing service. The team should include reproductive specialists, embryologists, clinical geneticists, genetic counsellors, cytogeneticists and molecular geneticists. It should maintain close contact with the primary care physician.
- 9.2** Treatment should include patient support following embryo testing.

#### The use of PGS

##### Interpretation of mandatory requirements

9A

An embryo may be tested to establish whether it has a particular chromosomal abnormality only if:

- a) that abnormality may affect its capacity to result in a live birth, or
- b) there is a particular risk that it has that abnormality, and where the Authority is satisfied that there is a significant risk that a person with that abnormality will have or develop a serious medical condition.

An embryo may be tested for PGS and PGD where the requirements for each have been satisfied before testing is carried out. Fulfilling the requirements for PGS does not act as a gateway to carrying out PGD, and vice versa.

- 9.3** The centre should ensure that before people seeking treatment give consent to PGS for aneuploidy, they are given information explaining:
- (a) the **procedure and** risks associated with the procedure
  - ~~(b) the unproven nature of the procedure, in particular that:~~
    - ~~(i) more robust clinical and laboratory trials are needed to assess whether or not PGS can significantly increase live birth rates~~
    - ~~(ii) the method of fluorescent in situ hybridisation (FISH) on embryos, using a limited number of chromosomes, is not effective at increasing live birth rates~~
  - (b) that more robust clinical and laboratory trials are needed to assess whether or not PGS can significantly increase live birth rates**
  - ~~(c) that embryos biopsied may not be available for cryopreservation and for use in subsequent treatment cycles~~
  - (c) the **failure and** misdiagnosis rates associated with PGS for aneuploidy, including the fact that false results can be positive or negative
  - ~~(d) that the more chromosome tests are carried out, the higher the possibility of the test not working and the lower the chance of finding suitable embryos for transfer~~
  - (d) the concept of mosaicism, and the effect that this could have on the accuracy of results**
  - (e) that PGS techniques are capable of detecting segmental aneuploidies which may generate results where the clinical significance is not known**
  - (f) that there is no guarantee against a miscarriage occurring, despite PGS for aneuploidy being performed, and
  - (g) the financial and emotional costs where treatment fails and there is no live birth following PGS for aneuploidy.
- 9.4** Before providing PGS, the centre should ensure that those seeking treatment have had sufficient opportunity to fully consider the possible outcomes and their implications.

- 9.5** Embryos from which biopsies have been taken, or resulting from gametes from which biopsies have been taken, should not be transferred with any other (non-biopsied) embryos in the same treatment cycle.
- ~~**9.3** Centres should ensure that they keep up to date with relevant literature and professional guidance in order to validate the use of PGS for each category of patient to which they offer it. Validation should also be based on data from previously published studies and retrospective evaluation of the clinic's own data.~~
- 9.6** Where patients seek PGS, but do not wish to be informed of any additional genetic information that may be found via sophisticated genetic testing methodologies (eg, segmental aneuploidies), where possible, guidelines around PGD for non-disclosure (paragraphs 10.10-10.12) should be adhered to.

See also:

Guidance note 10 – Embryo testing and sex selection

#### PGS and counselling

- 9.7** Where PGS is carried out using technologies that give rise to additional genetic information, the centre should ensure that people seeking treatment have access to clinical geneticists, genetic counsellors and, where appropriate, infertility counsellors before and after treatment has occurred.
- 9.8** The centre should work closely with the local genetics team of those seeking treatment.

#### Prohibitions on embryo selection

##### Interpretation of mandatory requirements

9B

The law requires that the centre should not select embryos of a particular sex for social reasons.

NOTE: Guidance note 10 (Embryo testing and sex selection) contains all the guidance and mandatory requirements relevant to embryo testing in general. Centres offering PGS should familiarise themselves with this guidance note as well.

#### Other legislation, professional guidelines and information

Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics – Consent and confidentiality in clinical generic practice: Guidance on genetic testing and sharing genetic information (A report of the Joint Committee on Medical Genetics)

Association for Clinical Genetic Science – Practice guidelines for targeted next generation sequencing analysis and interpretation



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## Annex B: Proposed amendments to guidance note 10: Embryo testing and sex selection

### Mandatory requirements

Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

*Schedule 2 – Activities that may be licensed under the 1990 Act*

*Licences for treatment*

*Embryo testing*

- 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,
  - (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,
    - ...
  - (e) in a case where uncertainty has arisen as to whether the embryo is one of those whose creation was brought about by using the gametes of particular persons, establishing whether it is.
- (2) A licence... 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.

- (3) For the purposes of sub-paragraph (1)(c), a physical or mental disability, illness or other medical condition is gender-related if the Authority is satisfied that–
- (a) it affects only one sex, or
  - (b) it affects one sex significantly more than the other.

#### Licence conditions

- T86 Embryos that are known to have a gene, chromosome or mitochondrion abnormality involving a significant risk that a person with the abnormality will have or develop:
- a. a serious physical or mental disability
  - b. a serious illness, or
  - c. any other serious medical condition, must not be preferred to those that are not known to have such an abnormality.
- T87 Embryos that are known to be of a particular sex and are known to carry a particular risk, compared with embryos of that sex in general, that any resulting child will have or develop:
- a. a gender-related serious physical or mental disability
  - b. a gender-related serious illness, or
  - c. any other gender-related serious medical condition, must not be preferred to those that are not known to carry such a risk.
- T88 With respect to any embryo testing programme involving biopsy the centre must ensure that:
- a. no embryo is transferred to a woman where that embryo or any material removed from it or from the gametes that produced it, has been subject to a test that supplies genetic information about the embryo, unless the test has been expressly authorised by the Authority, and
  - b. any information derived from tests on an embryo, or any material removed from it or from the gametes that produced it, is not used to select embryos of a particular sex for social reasons.
- T89 With respect to any embryo testing programme the centre must ensure that embryo testing is only being carried out for those genetic conditions that are expressly authorised by the Authority.
- 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.

### Directions

0008 – Information to be submitted to the HFEA as part of the licensing process

0012 – Retention of records

### HFEA Guidance

#### Staff to be involved in embryo testing

- 10.1** A senior clinical geneticist should be involved in deciding whether a particular patient should receive treatment involving embryo testing.
- 10.2** The centre should ensure that a multidisciplinary team is involved in providing the embryo testing service. The team should include reproductive specialists, embryologists, clinical geneticists, genetic counsellors, cytogeneticists and molecular geneticists. It should maintain close contact with the primary care physician or the referring clinician.
- 10.3** Treatment should include patient support following embryo testing.

#### Embryo transfer using biopsied embryos

- 10.4** Embryos from which biopsies have been taken, or resulting from gametes from which biopsies have been taken, should not be transferred with any other (non-biopsied) embryos in the same treatment cycle.

#### Preimplantation genetic diagnosis for heritable conditions

##### Interpretation of mandatory requirements

10A

Preimplantation genetic diagnosis (PGD) can be carried out for a heritable condition only in two circumstances:

- where there is a particular risk that the embryo to be tested may have a genetic, mitochondrial or chromosomal abnormality, and the Authority is satisfied that a person with the abnormality will have or develop a serious disability, illness or medical condition, or
- where there is a particular risk that any resulting child will have or develop a gender related serious disability, illness or medical condition. A condition is gender related if the Authority is satisfied that it affects only one sex, or affects one sex significantly more than the other. In the first situation, PGD may be carried out to establish whether the embryo has the suspected abnormality; in the second, PGD may be carried out to establish the sex of the embryo.

An embryo may be tested for PGS and PGD where the requirements for each have been satisfied before testing is carried out. Fulfilling the requirements for PGS does not act as a gateway to carrying out PGD, and vice versa.

- 10.5** When deciding if it is appropriate to provide PGD in particular cases, the centre should consider the circumstances of those seeking treatment rather than the particular heritable condition.
- 10.6** The use of PGD should be considered only where there is a significant risk of a serious genetic condition being present in the embryo. When deciding if it is appropriate to provide PGD in particular cases, the seriousness of the condition

in that case should be discussed between the people seeking treatment and the clinical team. The perception of the level of risk for those seeking treatment will also be an important factor for the centre to consider.

- 10.7** In instances where a patient is undergoing PGD for a heritable condition, a centre may offer PGD for additional condition(s) that do not meet the particular risk requirements but have been deemed, by the Authority, to be of significant risk. Consent should be taken and recorded in patient notes.
- 10.8** In instances where a patient is undergoing PGD for a heritable condition, a centre may offer preimplantation genetic screening (PGS) at the same time in accordance with guidance note 9. Consent should be taken and recorded in patient notes.
- 10.9** 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.
- 10.10** Concerns have been raised about the ethical implications of directly testing embryos for a genetic condition without disclosing the test results to the patients (PGD with non-disclosure).

Where patients seek PGD, but do not wish to discover their own genetic status, centres should, where possible, only offer PGD with exclusion testing.

Where patients seek PGD, but do not wish to be informed of any additional genetic information that might occur via sophisticated genetic testing methodologies (eg, segmental aneuploidies), where possible, PGD with exclusion testing should be offered and recorded.

- 10.11** In exceptional circumstances the centre may offer PGD, but withhold the patient's test results (PGD with non-disclosure). However, this should only be offered under the following conditions:
- (a) that patients are given the opportunity to receive genetic counselling on the implications prior to giving consent,
  - (b) that protocols are established to limit, as far as possible, the risk of unwanted disclosure to the patients. Centres should consider using a different embryology laboratory from their own, in order to minimise the number of centre staff who know the patient's genetic status, and
  - (c) that no dummy embryo transfers are to be performed.
- 10.12** The centre should document its reasons for offering PGD with non-disclosure to a patient. This record should include:

- (a) written informed consent from the patient to perform PGD with non-disclosure,
- (b) a statement from the people seeking treatment confirming that they have been given the opportunity to receive genetic counselling and that they have, prior to giving consent, received information:
  - (i) on the risks of inadvertent disclosure,
  - (ii) that where all embryos are suitable for transfer this is not evidence of the patient's genetic status,
  - (iii) that where no embryos are suitable for transfer this is not evidence of the patient's genetic status,
  - (iv) that therefore dummy embryo transfers are not necessary or permissible, and
  - (v) that treatment may go ahead which is not medically necessary in cases where the patient (or partner) does not have the genetic condition. This includes information about the potential costs and risks of any medically unnecessary treatments.

#### Preimplantation genetic diagnosis to establish the identity of gamete providers

##### Interpretation of mandatory requirements

10B

An embryo may be tested to establish whether it was brought about using the gametes of particular people, where this is uncertain.

#### Genetic consultation and counselling

**10.13** The centre should ensure that people seeking treatment have access to clinical geneticists, genetic counsellors and, where appropriate, infertility counsellors **before and after treatment has occurred.**

**10.14** The centre should work closely with the local genetics team of those seeking treatment.

#### Information for those seeking preimplantation genetic diagnosis

**10.15** The centre should ensure that people seeking PGD are given the appropriate information about the treatment. This should include:

- (a) the process, procedures and possible risks involved in IVF and biopsy procedures when providing a sophisticated genetic test.
- (b) the experience of the centre in carrying out the procedure.
- (c) **that sophisticated genetic tests can reveal additional genetic information about an embryo(s) and that the clinical effect of these findings on a child born may not be known.**

**10.16** The centre should also provide information to those seeking treatment to help them make decisions about their treatment, including:

- (a) genetic and clinical information about the condition being tested for
- (b) the likely impact of the condition on those affected and their families
- (c) information about treatment and social support available, and
- (d) information from a relevant patient support group or the testimony of people living with the condition, if those seeking treatment have no direct experience of it themselves.

- 10.17** If the person seeking treatment has already been given information about the particular genetic disorder, for example from a regional genetics centre, the centre need not provide this information again. However, the centre should ensure that the information has been provided to a satisfactory standard of breadth and clarity.
- 10.18** Before providing PGD, the centre should ensure that those seeking treatment have had sufficient opportunity to fully consider the possible outcomes of genetic testing and their implications.

#### Prohibitions in connection with embryo selection

### Mandatory requirements

#### Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

#### Section 13

- (8) Subsections (9) and (10) apply in determining any of the following –
- (a) the persons who are to provide gametes for use in pursuance of the licence in a case where consent is required under paragraph 5 of Schedule 3 for the use in question;
  - (b) the woman from whom an embryo is to be taken for use in pursuance of the licence, in a case where her consent is required under paragraph 7 of Schedule 3 for the use of the embryo;
  - (c) which of two or more embryos to place in a woman.
- (9) Persons or embryos that are known to have a gene, chromosome or mitochondrion abnormality involving a significant risk that a person with the abnormality will have or develop–
- (a) a serious physical or mental disability,
  - (b) a serious illness, or
  - (c) any other serious medical condition, must not be preferred to those that are not known to have such an abnormality.
- (10) Embryos that are known to be of a particular sex and to carry a particular risk, compared with embryos of that sex in general, that any resulting child will have or develop–
- (a) a gender-related serious physical or mental disability,
  - (b) a gender-related serious illness, or
  - (c) any other gender-related serious medical condition,
- must not be preferred to those that are not known to carry such a risk.

- (11) For the purposes of subsection (10), a physical or mental disability, illness or other medical condition is gender-related if—
- (a) it affects only one sex, or
  - (b) it affects one sex significantly more than the other.

*Schedule 2 – Activities that may be licensed under the 1990 Act*

*Sex selection*

- 1ZB (1) A licence under paragraph 1 cannot authorise any practice designed to secure that any resulting child will be of one sex rather than the other.
- (2) Sub-paragraph (1) does not prevent the authorisation of any testing of embryos that is capable of being authorised under paragraph 1ZA.
- (3) Sub-paragraph (1) does not prevent the authorisation of any other practices designed to secure that any resulting child will be of one sex rather than the other in a case where there is a particular risk that a woman will give birth to a child who will have or develop—
- (a) a gender-related serious physical or mental disability,
  - (b) a gender-related serious illness, or
  - (c) any other gender-related serious medical condition.
- (4) For the purposes of sub-paragraph (3), a physical or mental disability, illness or other medical condition is gender-related if the Authority is satisfied that—
- (a) it affects only one sex, or
  - (b) it affects one sex significantly more than the other.

**Licence conditions**

- T86 Embryos that are known to have a gene, chromosome or mitochondrion abnormality involving a significant risk that a person with the abnormality will have or develop:
- a. a serious physical or mental disability
  - b. a serious illness, or
  - c. any other serious medical condition,
- must not be preferred to those that are not known to have such an abnormality.
- T87 Embryos that are known to be of a particular sex and are known to carry a particular risk, compared with embryos of that sex in general, that any resulting child will have or develop:

- a. a gender-related serious physical or mental disability
- b. a gender-related serious illness, or
- c. any other gender-related serious medical condition,

must not be preferred to those that are not known to carry such a risk.

T88 With respect to any embryo testing programme involving biopsy the centre must ensure that:

...

- b. any information derived from tests on an embryo, or any material removed from it or from the gametes that produced it, is not used to select embryos of a particular sex for social reasons.

#### Interpretation of mandatory requirements

10C

The law prohibits the selection of an embryo for treatment if it is known to:

- a) have a gene, chromosome or mitochondrial abnormality involving a significant risk that the person with the abnormality will develop a serious physical or mental disability, a serious illness, or a serious medical condition, or
- b) be of a sex that carries a particular risk that any resulting child will have or develop a gender-related serious physical or mental disability, serious illness, or serious medical condition.

This applies only where there is at least one other embryo suitable for transfer that is not known to have the characteristics. Where there is no other embryo suitable for transfer, an embryo with these characteristics may be transferred.

**10.19** The use of an embryo known to have an abnormality as described above should be subject to consideration of the welfare of any resulting child and should normally have approval from a clinical ethics committee.

**10.20** If a centre decides that it is appropriate to provide treatment services to a woman using an embryo known to have an abnormality as described above, it should document the reason for the use of that embryo.

NOTE: An example of an embryo not suitable for transfer in this context is one that has no realistic prospect of resulting in a live birth.

See also:

Guidance note 8 – Welfare of the child

#### Sex selection for social reasons

#### Interpretation of mandatory requirements

10D

The law requires that the centre should not, for social reasons:

- a) select embryos of a particular sex
- b) separate sperm samples, or use sperm samples that have been separated, for the purpose of sex selection, or
- c) participate in any other practices designed to ensure that a resulting child will be of a particular sex.



### Sex selection: sperm sorting for medical reasons

- 10.21** If sperm is sorted for medical reasons to create (or maximise the chance of creating) embryos of a particular sex for medical reasons, patients should be given information about the process, procedures, possible risks and the experience of the clinic in doing the procedure.
- 10.22** Due to concerns about the reliability of the technique, sperm that has been sorted for sex selection using gradient methods should not be used for medical reasons.

### Preimplantation genetic diagnosis for histocompatibility (tissue typing)

#### Mandatory requirements

Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

*Schedule 2 – Activities that may be licensed under the 1990 Act*

*Licences for treatment*

*Embryo testing*

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

...

(d) in a case where a person (“the sibling”) who is the child of the persons whose gametes are used to bring about the creation of the embryo (or of either of those persons) suffers from a serious medical condition which could be treated by umbilical cord blood stem cells, bone marrow or other tissue of any resulting child, establishing whether the tissue of any resulting child would be compatible with that of the sibling

...

- 1ZA (4) In sub-paragraph (1)(d) the reference to “other tissue” of the resulting child does not include a reference to any whole organ of the child.

#### Interpretation of mandatory requirements

10E

The law requires that the intended recipient of any donated tissue from a child born following tissue typing must:

- be a sibling of any child born as a result of treatment, and
- suffer from a serious medical condition that could be treated by umbilical cord blood stem cells, bone marrow or other tissue (excluding whole organs) of any resulting child.

The law also permits tissue typing if the embryo will not, in addition to the histocompatibility test, be tested for a particular genetic or mitochondrial abnormality.

- 10.23** Where preimplantation tissue typing is to be used with PGD for a heritable condition, the centre should follow the requirements and guidance applicable to a PGD service.
- 10.24** When deciding whether to use preimplantation tissue typing, the centre should consider the circumstances of each case individually, rather than the fact that the procedure is sought to provide tissue to treat a particular condition.
- 10.25** When deciding on the appropriateness of preimplantation tissue typing in a particular situation, the centre should consider the condition of the affected child, including:
- (a) the degree of suffering associated with their condition
  - (b) the speed of degeneration in progressive disorders
  - (c) the extent of any intellectual impairment
  - (d) their prognosis, considering all treatment options available
  - (e) the availability of alternative sources of tissue for treating them, now and in the future, and
  - (f) the availability of effective therapy for them, now and in the future.
- 10.26** The centre should also consider the possible consequences for any child who may be born as a result, including:
- (a) any possible risks associated with embryo biopsy
  - (b) the likely long-term emotional and psychological implications
  - (c) whether they are likely to require intrusive surgery as a result of the treatment of the affected child (and whether this is likely to be repeated), and
  - (d) any complications or predispositions associated with the tissue type to be selected.
- 10.27** The centre should also consider the family circumstances of the people seeking treatment, including:
- (a) their previous reproductive experience
  - (b) their views and the affected child's views of the condition
  - (c) the likelihood of a successful outcome, taking into account:
    - (i) their reproductive circumstances (ie, the number of embryos likely to be available for testing in each treatment cycle, the number likely to be suitable for transfer, whether carrier embryos may be transferred, and the likely number of cycles)
    - (ii) the likely outcome of treatment for the affected child
  - (d) the consequences of an unsuccessful outcome
  - (e) the demands of IVF/preimplantation testing treatment on them while caring for an affected child, and
  - (f) the extent of social support available.

#### Information for those seeking preimplantation genetic diagnosis for histocompatibility

- 10.28** Information given to patients considering preimplantation tissue typing should include:
- (a) information about the tissue typing tests to be done

- (b) an explanation of the latest evidence about any risk associated with the biopsy procedure for any child who may be born
- (c) the overall likelihood of a successful outcome for the affected child, including:
  - (i) the likelihood of an embryo with appropriate tissue type being available for transfer following the IVF, biopsy and genetic testing
  - (ii) the likelihood of a child being born as a result, taking into account the circumstances of the people seeking treatment and their previous reproductive experience
  - (iii) the likelihood of tissue from that child providing a successful treatment
  - (iv) the limitations of the treatment for the affected child
- (d) the likely impact of the proposed procedure on all family members involved, and
- (e) information about other sources of treatment, counselling and social support available.

**10.29** If information about the disorder affecting the existing child has already been provided, for example by a regional genetics centre or by the clinical team responsible for that child's care, it will not be necessary to provide this information again. However, the centre should:

- (a) ensure that this information is satisfactorily broad and clear, and
- (b) obtain a statement to that effect from those providing it.

#### Follow-up arrangements for preimplantation tissue typing

**10.30** Centres offering preimplantation tissue typing should be able to demonstrate that they have arrangements for inviting patients and their families to take part in long-term follow-up studies. These should include long-term medical and psychosocial follow-up studies of children born as a result. Centres should strongly encourage patients and their families to participate in such studies.

See also:

Guidance note 5 – Consent to treatment, storage, donation and disclosure of information

HFEA consent forms

#### Other legislation, professional guidelines and information

Association of Clinical Embryologists – Accreditation Standards and Guidelines for IVF Laboratories

Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics – Consent and confidentiality in clinical genetic practice: Guidance on genetic testing and sharing genetic information (A report of the Joint Committee on Medical Genetics)

Association for Clinical Genetic Science – Practice guidelines for targeted next generation sequencing analysis and interpretation