

**HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY**  
**ETHICS & LAW ADVISORY COMMITTEE**

|   |   |
|---|---|
| <b>Committee:</b>                       | Ethics & Law Advisory Committee   |
| <b>Meeting Date:</b>                    | 15 <sup>th</sup> December 2009  |
| <b>Agenda Item:</b>                     | 8   |
| <b>Paper Number:</b>                    | ELAC (12-09) 3  |
| <b>Paper Title:</b>                     | Case by case decision making in PGD   |
| <b>Author:</b>                          | Danny Edwards, Policy Manager   |
| <b>For Information or Decision?</b>     | Decision  |
| <b>Resource Implications:</b>           | None  |
| <b>Recommendation to the Committee:</b> | <p>Members are asked to consider the issues raised in this paper and provide recommendations to the Authority:</p> <ul style="list-style-type: none"> <li>▪ Which of the described methods for licensing later onset, lower penetrance conditions is preferred (with any caveats/modifications)</li> <li>▪ Which of the described methods of licensing preimplantation tissue typing is preferred (with any caveats/modifications)</li> </ul> |

## 1 Introduction

1.1 This paper asks for the views of the Ethics and Law Advisory Committee (ELAC) regarding proposed alternatives for licensing categories of preimplantation genetic diagnosis (PGD) which are currently considered by the Authority on a case by case basis. These are:

- Testing embryos for mutations where a person with that mutation would be at risk of a later onset, lower penetrance condition,
- Preimplantation tissue typing of embryos (PTT).

The views of ELAC will be used to inform final recommendations for Authority decision in January 2010.

1.2 When the Authority last conducted reviews of the licensing of later onset, lower penetrance conditions and PTT (in May 2006, and December 2004, respectively), the Authority in both instances committed to reviewing the licensing process once evidence and experience had accumulated.

1.3 Further reasons to review have been:

- Over the intervening period (both through consultation events and discussions with centre staff) affected parties have stated that the case by case approach slows down access to treatment in cases where timing is particularly sensitive,

- Provisions of the Human Fertilisation and Embryology Act 2008 on PGD are now in force, and stemming from this we have in place a redesigned procedure for licensing PGD.

1.4 In reviewing the case by case policies, this project has gathered evidence from:

- The documents pertaining to case by case licensing decisions (application forms, peer reviews, and Licence Committee minutes) and the experience of Members who sat on Licence Committees considering case by case applications,
- The views of external experts, namely cancer geneticists and consultant haematologists/ consultant paediatricians,
- A consultation event held on 1 December 2009, attended by 37 people, comprising a mix of patient groups, clinicians and other interested parties.

1.5 The aim of this review has been to identify and investigate the rationales for licensing these categories of embryo testing on a case by case basis and to evaluate whether the reasons for continuing without change still stand. A further focus has been to ensure that the licensing process for embryo testing remains robust, efficient and proportionate.

## **2 Existing HFEA regulation of embryo testing**

2.1 On 1 October 2009, the Human Fertilisation and Embryology Act 2008 (the 2008 Act) came into force, amending the Human Fertilisation and Embryology Act 1990. The amendments in the 2008 Act set out that embryo testing must be licensed by the HFEA, and details the statutory tests to be satisfied before licences are issued. The relevant paragraphs of the Act are attached at Annex A. In summary, when licensing PGD, the Authority must be satisfied that:

- There is a particular risk that the embryo being tested will have the abnormality that it is being tested for,
- There is a significant risk that a person with that abnormality will have, or will develop a condition,
- That the condition is serious.

2.2 The amendments in the Act prompted a redesign of the PGD licensing process. In this redesign, the Authority sought advice from external legal counsel.

2.3 Legal advice received set out that it is for the Authority to be satisfied of the statutory requirements of risk and seriousness. The advice also set out that this may be on a condition by condition basis. The statute does not require a case by case assessment of PGD applications. This in principle approach has now been applied to most PGD applications. Equally, it could be applied to later onset, lower penetrance conditions and PTT, so long as the statutory requirements are satisfied and the Authority agreed that this constituted sufficient oversight for this category of cases.

2.4 Key elements of the updated licensing process are:

- If a clinic licensed to perform embryo testing wishes to offer PGD for a condition not previously approved they must apply to the Licence Committee, setting out how they consider the condition meets the statutory requirements,
  - That the Licence Committee also considers evidence from independent peer reviewers and relevant patient groups. If the licence is granted, any clinic licensed for PGD in the United Kingdom is able to test for that condition. A licence condition (T89) restricts PGD centres to testing for authorised conditions,
  - Code of Practice guidance advises clinics to carry out PGD in particular cases only where there is a significant risk of a serious condition being present in the embryo.
- 2.5 This process creates a two-tier judgement – the Authority must be satisfied in general of the requirements for risk and seriousness for each condition, whereas centres are advised to make judgements about the appropriateness of PGD given the clinical history and experience of a particular family.
- 2.6 However, for later onset, lower penetrance conditions, both applications to test for a novel condition and applications to test for conditions previously licensed are considered by the Licence Committee. These applications are submitted using the application form attached at Annex B.
- 2.7 For PTT applications novel conditions are considered by the Licence Committee. Each subsequent application for previously licensed conditions is considered by the Executive Licensing Panel (ELP), a decision-making body comprised of senior executive staff.<sup>1</sup> Applications for PTT are also submitted on the form at Annex B; an additional requirement is that a letter from the affected sibling's treating clinician needs to be included.

---

<sup>1</sup> Note that the ELP meets once a fortnight, whereas the Licence Committee meets once a month. Items sent to the ELP can be viewed more rapidly.

### 3 Later onset, lower penetrance conditions

#### *Background*

##### What are later onset, lower penetrance conditions?

It is possible to use PGD to test embryos for the presence of genes that result in an increased predisposition to a condition, often cancer. These include tests for increased susceptibilities to forms of ovarian, breast and bowel cancer. The Authority has considered conditions to fall into this category if they meet the following criteria:

- They are lower penetrance
- They have a later age of onset (often in adult life)
- There is a possibility for preventative surgery, early detection and effective treatment for these cancers in susceptible individuals.

Though the conditions licensed so far usually involve increased predispositions to cancer, other conditions which meet the criteria would be considered in the same way.

##### Penetrance

Penetrance is a population-based statistic which describes what percentage of individuals in a population with a mutation in a gene will develop the condition associated with that mutation. It does not identify who will develop the condition.

##### Mode of inheritance

The manner in which a genetic mutation is passed from one generation to the next. Examples of modes are Autosomal dominant and Autosomal recessive. The mode of inheritance defines the probability of a child inheriting a mutation.

#### *Existing policy*

- 3.1 In 2005, the HFEA conducted a policy review to consider licensing tests for genetic susceptibility to disease. This included a public event and an invitation for written submissions.
- 3.2 The results of this review were taken to the Authority's Ethics and Law Committee (ELC). In summary, ELC recommended to the Authority that:
  - The penetrance of a condition is not the only factor that determines significant risk, although it is relevant. Also important is how the risk is perceived by a person seeking treatment. For very serious conditions, even a lower risk of penetrance can be perceived as unacceptable to a person seeking treatment.
  - The facts that conditions may be later onset, have a lower penetrance and are in some cases treatable is not necessarily incompatible with the fact that these are serious genetic conditions.

- 3.3 The Authority decided in June 2006 that it was acceptable for a Licence Committee to licence later onset, lower penetrance conditions. The Authority agreed at this time that significant risk should be established on an overall basis, through combining an assessment of penetrance, seriousness and a family's experience of the condition.<sup>2</sup>
- 3.4 The Authority held however, that licensing of later onset, lower penetrance conditions should proceed on a case by case basis, with a review to be carried out once evidence and experience had accumulated.
- 3.5 The rationales for licensing later onset, lower penetrance conditions on a case by case basis were two-fold:
- They constituted a new category of condition for use in PGD, and initial caution was prudent,
  - Families were affected differently by these conditions through the possibility of genetic variation.

*What has happened in practice?*

- 3.6 The Authority (as of December 2009) has licensed six later onset, not fully penetrant conditions on a case by case basis. These are:

| Condition              | Age of onset                                    | Penetrance   | Description   | Mode of inheritance |
|------------------------|---|--|---|---------------------|
| BRCA1                  | 10-20 years earlier than sporadic breast cancer | 60-65% breast cancer<br>20% risk of ovarian cancer | Hereditary disposition to breast and ovarian cancers  | Autosomal dominant  |
| Carney complex         | Varies from childhood to adulthood              | High, with variable severity                       | Causes spotty skin pigmentation, myxomas (benign connective tissue tumours), and benign or cancerous tumours of the endocrine glands  | Autosomal dominant  |
| Lynch syndrome (HNPCC) | 40s, but may be younger                         | 80%  | Hereditary nonpolyposis colorectal cancer, site specific to the colon   | Autosomal dominant  |
| Tuberous sclerosis     | Varies  | High, with variable severity                       | Growths (tubers or lesions) in different organs of the body (brain, heart, eyes, skin, kidneys, lungs) can cause epilepsy, learning disabilities, autism spectrum disorder and kidney problems. | Autosomal dominant  |

<sup>2</sup> The 2008 Act requires that a Licence Committee be satisfied of 'significant risk' and 'seriousness' prior to licensing a condition in general. Guidance exists for the Licence Committee regarding establishing seriousness. A separate piece of work has been proposed, to develop guidance on the consideration of 'significant risk.'

|  |                        |                              |   |                     |
|--|------------------------|------------------------------|---|---------------------|
| Cystinosis                               | 2-20s (normally 12-13) | High, with variable severity | Mechanism for removing excess cystine breaks down. Cystine accumulates, causing damage to organs such as the kidneys, eyes, pancreas and brain. | Autosomal recessive |
| Hereditary diffuse gastric cancer (HDGC) | Late 30s               | 67% men<br>83% women         | Inherited cancer-susceptibility for gastric cancers and in women lobular breast cancer  | Autosomal dominant  |

3.7 Eight case by case licences have been issued for these conditions since 2006: three for BRCA1, and one each for the remaining five conditions.

### *Evidence*

#### Licensing evidence

3.8 The Executive reviewed the documents pertaining to licensing decisions for later onset, lower penetrance conditions (the application form, peer review and, Committee minutes). Key points from the analysis of the licensing documentation:

- Across the three BRCA1 decisions, in each case the severity of the condition, the mode of inheritance, and the penetrance were noted and were the same.
- HNPCC, HDGC and Carney complex and applications, the risk of the embryo having the mutation, the mode of inheritance, the penetrance, and the severity of the condition were sufficient to grant the licence.
- Applications for cystinosis and tuberous sclerosis similarly described the inheritance pattern. These applications sit slightly apart from the others in that they are both highly penetrant conditions. Some features of tuberous sclerosis are early onset, and in the case of cystinosis age of onset can vary widely. These two conditions exhibit significant variability in the severity<sup>3</sup> of the condition between individuals. This potential for variation is captured in the documents considered by the Licence Committee.
- In two cases for BRCA1 applications it had taken 50 working days (10 weeks) for a decision to be made.

3.9 Furthermore, four members of the Authority with experience of these licensing decisions were asked for their comments on the quality a case by case approach has lent to decisions about later onset, lower penetrance applications. Members pointed out that case by case decision making required judging the experience of risk and seriousness for a particular family, which was felt to be difficult. The lack of variation of mode of inheritance was also pointed out. A benefit of the case by

<sup>3</sup> Also described as the expressivity of a condition: the degree to which a particular condition manifests in an individual.

case approach was felt to be the opportunity it provided to ensure that the centre had provided adequate counselling and information.

3.10 It should be noted that the existing evidence to draw on, and Member experience of these licensing decisions remains very limited. The Executive also consulted experts in cancer genetics to see what sort of variation we might encounter between future cases.

#### Expert opinion

3.11 The Executive sought the expertise of five geneticists. They were asked whether there are significant differences between the families with later onset, lower penetrance conditions which might justify a case by case approach.

3.12 Summary of evidence received from geneticists:

- Penetrance gives a statistical likelihood of the risk of developing the condition and cannot be broken down for individual families. Risk information can therefore not be tailored to an individual family.<sup>4</sup>
- The mode of inheritance and the penetrance does not vary between cases.
- There has been a low uptake of PGD for people with mutations in BRCA1. This was linked to the relatively small window of opportunity to have a child that a person with BRCA1 has before preventative mastectomy/oophorectomy might take place.

#### Consultation event

3.13 A consultation event was held on 1 December 2009 in London. It was attended by 37 people (mostly centre staff, but also patient group representatives and other interested parties).

3.14 Summary of evidence received from the consultation event:

- A clear majority view that the HFEA should move away from case by case licensing of later onset, lower penetrance conditions. Wide support for a scheme where licensed PGD centres could test for any condition previously licensed and compliance monitored on inspection.
- A view emerged that if the reason for case by case licensing is to give the public reassurance that embryo testing was being regulated, then this is perhaps not best addressed by making case by case decisions where there was little difference between applicants.

---

<sup>4</sup> The conditions that have been licensed by the Authority to date have an established penetrance (or, where unknown, a high penetrance), and hence known risk information for affected families to consider.

- Case by case licensing can impact on the timing of a PCT decision to fund treatment – they will sometimes wait until the HFEA has granted a licence.
- However, a delegate raised concerns that there was not yet enough evidence accumulated for lower penetrance conditions to move away from the original case by case approach. It was argued that the lower penetrance and later age of onset of these conditions meant questions remained about the 'seriousness' of these conditions. Finally, it was stated that patients can exert pressure on clinicians and that this is a reason that it is better to have decisions made by the HFEA.

### *Summary of findings*

- 3.15 Evidence from existing licensing decisions, while limited, has demonstrated that there is little variation between applications to test for later onset, lower penetrance conditions. Views from experts in cancer genetics and the participants of the stakeholder workshop echoed this assessment.
- 3.16 It is important to identify that the majority of delegates at the consultation event were PGD centre staff, all of whom shared a similar point of view about licensing. Those who disagreed with the delegation of case by case decisions to PGD centre staff were concerned about the broader public interest in regulation of embryo testing, and that independent regulation of embryo testing remains essential. Were the Authority to stop its case by case approach to licensing these conditions, another safeguard might need to be found for reassuring the public that regulatory oversight had not been lost.

### *Analysis and policy alternatives*

- 3.17 In addressing the evidence before the Authority, the Committee needs to clearly weigh up two perspectives:
- The need for public reassurance that regulatory oversight over this still relatively new category of PGD testing is maintained,
  - The need to sustain a meaningful licensing process which does not impose unnecessary burdens on clinic staff and those affected by genetic conditions.
- 3.18 The evidence gathered by the Executive shows that case by case licensing has been helpful for identifying the types of conditions this approach applies to and for establishing publicly and transparently the limited variability with which these conditions are assessed by clinicians and by the Authority.
- 3.19 ELAC is reminded that we have in place a rigorous new process for PGD licensing, which requires two levels of assessment: The Authority needs to ascertain that the statutory requirements for risk and seriousness are principally met for a given condition; the clinician is then also tasked with ensuring that PGD is only offered in cases of significant risk of a serious condition.

3.20 It is worth noting, however, that this requirement of clinics is only expressed in the form of Code of Practice guidance, ie it is less enforceable than mandatory requirements, for example Licence Conditions.

3.21 Decisions about the appropriateness of PGD in particular circumstances are made by PGD centre staff, using guidance in the HFEA Code of Practice which sets out:

**10.5** 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.

3.22 In addressing the question of case by case licensing, the Committee might therefore consider other regulatory options like elevating current Code of Practice guidance to the status of a mandatory licence condition.

3.23 Such a Licence Condition could apply to all PGD testing, not just lower penetrance, late onset conditions, and would thus also take account of the also now better established fact that other conditions currently licensed under the general licensing regime also have a wider range of symptoms and ages of onset than was perhaps previously recognised.

3.24 This would *require* PGD centres, for each case, to be satisfied that:

- The embryo is at risk of inheriting a particular mutation
- The condition is serious in that case
- A person with that mutation is at risk of developing a serious genetic condition.

3.25 These could be included in both the inspection notebook, and the Self Assessment Questionnaire (SAQ). The Authority would be able to monitor the use of PGD in particular cases through both the SAQ and on inspection.

3.26 Based on this scheme, PGD could then only be carried out for authorised conditions, and only in particular families at risk of passing on a heritable mutation connected to a serious condition. If a centre used PGD inappropriately this would be considered a breach of a licence condition.

3.27 On the following page four options have been set out for the future licensing of later onset, lower penetrance conditions, alongside the identified benefits and drawbacks of each.

| Options  | Benefit  | Drawback  |
|--|--|---|
| <p><b>1. Continue licensing applications on a case by case basis.</b></p>  | <p>Ensures that tests are used appropriately, and only in those families at risk from the mutation.</p> <p>Maintains confidence that PGD in these cases is being regulated tightly, and not used for 'trivial reasons'</p>               | <p>Additional time taken to licence applications</p> <p>Regulatory burden without statutory requirement</p> <p>Little evidence of variability between applications.</p>   |
| <p><b>2. Continue licensing applications on a case by case basis, but delegate all but novel decisions to ELP.</b></p>   | <p>The delegation of subsequent decisions to the ELP may help to resolve concerns about the time the process takes.</p> <p>Maintains confidence that PGD is being regulated tightly, and not used for 'trivial reasons'</p>              | <p>Inconsistent with other forms of PGD licensing, when the statutory criteria to satisfy remain the same.</p> <p>Does not completely address time concerns of stakeholders.</p> <p>Stakeholders felt there as little real difference between option 1 and 2 and that ELP oversight might become merely 'symbolic.'</p> |
| <p><b>3. License on a condition by condition basis in line with general PGD.</b></p> <p>Clinicians would make decisions in particular patient cases about the appropriateness of PGD, <b>in line with Code of Practice guidance about risk and seriousness</b></p>             | <p>Consistent with general PGD licensing</p> <p>Addresses concerns about regulatory burden and time taken to consider applications</p>   | <p>Concern that loss of regulatory oversight might lead to PGD being used in a family inappropriately.</p> <p>Code of Practice guidance not mandatory and therefore harder to enforce.</p> <p>'Bad practice' might not be detected.</p>   |
| <p><b>4. Licence on a condition by condition basis only</b> but elevate Code of Practice guidance to a <b>new Licence Condition</b>, making it a mandatory requirement that clinics ensure that PGD is only used where there is a significant risk of a serious condition.</p> | <p>Addresses concerns about regulatory burdens</p> <p>Gives clinicians responsibility for assessing individual cases, but also makes this responsibility enforceable</p> <p>Might reduce concerns about loss of regulatory oversight</p> | <p>Authority loses prior access to information about the use of PGD for lower penetrance conditions.</p> <p>Potential that 'bad practice' might go undetected, before inspection occurs.</p>  |

3.28 Note that in options 3 and 4, as for other forms of PGD, the Licence Committee would retain the discretion to issue a one-off licence.

**3.29 ELAC is asked to consider these alternative policy options, and provide a recommendation to the Authority on their preferred approach, alongside any caveats and/or modifications.**

*Next steps*

3.30 The next step is for a paper to be taken to the Authority on 20 January for decision. The recommendations of ELAC will be used to inform that paper.

## 4 Preimplantation tissue typing

### *What is preimplantation tissue typing?*

Preimplantation tissue typing (PTT) uses the same techniques as PGD, but involves testing for the embryo's tissue type. This allows the selection of embryos which will be a tissue match with an existing sibling in need of a tissue transplant.

Tissue typing of embryos is most often carried out in combination with PGD to ensure that the child born does not inherit the condition. In some cases the condition the older sibling suffers from is not heritable, and in these cases PTT is carried out without PGD.

### *Background*

4.1 The Authority has conducted two policy reviews on the use of preimplantation tissue (PTT). In both cases there was thorough analysis by the Ethics and Law Committee. The existing policy is:

- PTT licenses must be issued case by case.
- Embryos may be tissue typed either in combination with a genetic testing step, or where tissue typing is the sole objective.
- The seriousness of the condition the existing child suffers from should be of a seriousness that would justify the use of PGD.
- The application to carry out PTT must be fully supported by the clinical team treating the sick child (usually a consultant haematologist). The child's clinical team would be expected to have considered the availability of alternative treatments and sources of tissue.

4.2 When considering whether or not to issue a licence for PTT, a Licence Committee considers the following aspects of the existing sibling's situation:

- The condition they suffer from (suffering, speed of degeneration)
- Their prognosis
- The availability of alternative sources of tissue for the treatment
- The availability of effective therapy

4.3 These aspects are addressed in a letter from the child's treating clinician, as required by the application form at Annex B.

4.4 The 2004 policy on tissue typing recommended that the risks to embryos from embryo biopsy be kept under review. In 2008, the Science and Clinical Advances

Advisory Committee (SCAAC) conducted a further literature review regarding these risks and were satisfied that there was still no evidence to suggest that embryo biopsy negatively affects the health of children born.

*The Human Fertilisation and Embryology Act 2008*

- 4.5 Among the amendments made to the 1990 Act is the inclusion of a provision which sets out that tissue typing is a licensable activity (see Annex A). This provision was subject to, and passed by, a free vote in the House of Commons on 19 May 2008.
- 4.6 The 2008 Act requires that the beneficiary of the donation be a sibling, that the existing sibling suffers from a *serious* condition, and that the condition can be treated through a donation from the child to be born. A further restriction is that tissue typing cannot be licensed in cases where the intent would be to use a whole organ of the resulting child. Cord blood stem cells, bone marrow, and other tissues are explicitly permitted.
- 4.7 It should be noted that the HFEA's remit extends to licensing the embryo testing leading to the creation of a tissue matched child. Later decisions about the donation of tissue receive the consideration of the Human Tissue Authority licensing process and the protection of common law.
- 4.8 While the 2008 Act is silent about the process that must be followed for licensing tissue typing, during the debates on PTT the then Minister for Public Health made the following comment:

*'...the HFEA has licensed tissue-typing only in a handful of cases, and always for life threatening conditions. It considers applications for the process on a case by case basis and we would expect it to continue on that basis.'*<sup>5</sup>

*What has happened in practice?*

- 4.9 To date, the Authority has licensed 10 conditions for which PTT has been deemed appropriate under the case by case regime. All conditions can be treated with a cord blood or bone marrow donation from an HLA-matched donor. They are:

| Condition           | Number of family applications | Heritable/sporadic | Description   |
|---------------------|-------------------------------|--------------------|---|
| Fanconi's Anaemia A | 2                             | Heritable          | Causes severe aplastic anaemia, hypoplasia of the bone marrow, and patchy discoloration of the skin.                                      |
| Fanconi's Anaemia C | 2                             | Heritable          | Causes severe aplastic anaemia, hypoplasia of the bone marrow, and patchy discoloration of the skin.                                      |
| Beta thalassaemia   | 10                            | Heritable          | Beta thalassaemia is a transfusion dependent anaemia requiring blood transfusions from infancy. The untreated lifespan is under 10 years. |
| Alpha thalassaemia  | 1                             | Heritable          | Alpha thalassaemia ranges from moderate to severe, and can similarly to beta thalassaemia, require blood transfusions.                    |

<sup>5</sup> House of Commons, *Parliamentary Debates*, May 19, 2008, column 107

|                                      |   |                        |   |
|--------------------------------------|---|------------------------|---|
| Diamond blackfan anaemia             | 4 | Heritable/<br>Sporadic | Congenital erythroid aplasia that usually presents in infancy. Approximately 30% to 40% of patients have other congenital anomalies, particularly of the upper limb and craniofacial regions.   |
| Wiscott-aldrich syndrome             | 1 | Heritable              | X-linked recessive immunodeficiency characterized by thrombocytopenia, eczema, and recurrent infections.  |
| X-linked hyper IgM Syndrome          | 1 | Heritable              | Rare immunodeficiency characterized by normal or elevated serum IgM levels with absence of IgG, IgA, and IgE, resulting in a profound susceptibility to bacterial infections and an increased susceptibility to opportunistic infections. |
| Leukocyte adhesion deficiency type 1 | 1 | Heritable              | Condition that affects the body's ability to fight infection and delays wound healing.  |
| Aplastic anaemia                     | 1 | Sporadic               | Damage to bone marrow stem cells resulting in fewer red and white blood cells and fewer platelets.  |
| Sickle cell anaemia                  | 1 | Heritable              | Result of mutant betaglobin in which the mutation causes sickling of haemoglobin.   |

4.10 In total 24 case by case licences have been issued for these conditions.

#### *Evidence*

#### Licensing evidence

4.11 The Executive reviewed the documents pertaining to licensing decisions for PTT. The documents included, for each application:

- The application form from the centre
- The peer review
- The Licence Committee minutes

4.12 Key points from the analysis of the licensing documentation:

- Of the 24 cases considered, the Authority has not yet turned down an application for tissue typing.
- The key variable factor between applications is the letter from the child's treating clinician.
- The assessment of the seriousness of the condition in the affected child for each successive case has been the same (where there were multiple cases of the same condition to examine).
- The licensing process has taken, in the cases examined, up to 10 weeks. Now that the Executive Licensing Panel (ELP) is examining previously licensed conditions, the process has taken up to one month.

4.13 Four members of the Authority with experience of these licensing decisions were asked for their comments on the quality a case by case approach has lent to decisions about PTT. The key points were:

- The variance from case to case lies in the specific features of the existing sibling's condition and treatment options. These have been satisfied by the letter from a treating clinician.
- Viewing each case has allowed us to maintain a central repository of all the information about these decisions, giving greater oversight.

#### Expert opinion

4.14 The Executive sought the expertise of four consultant haematologists when investigating the benefit of licensing PTT on a case by case basis. The consultant haematologists were asked about differences between each applicant case that would further inform the existing rationales for a case by case approach. Summary of evidence received from the consultants:

- There was concern about time taken for applications to be approved, causing distress for the families treated, heightened where the condition of the sibling was deteriorating.
- That it is difficult for families to access information about treatment, the possibility of success, risks and the time involved.
- That a case by case approach assists insofar as it allows for the opinion of a consultant haematologist regarding any variation in the severity of the disease for that child, whether or not the treatment would be effective for that child, and whether or not effective tissue was available.
- That there are a clear set of blood disorders where a transfusion from an HLA matched sibling is the most effective treatment (eg, Beta thalassaemia).

#### Consultation event

At the consultation event held on 1 December, participants were also asked for views about case by case licensing of PTT. Summary of evidence received from the consultation event:

- A clear majority thought that licensing of PTT should be on a condition by condition basis, in line with the general regime for PGD licensing. Indications for pursuing tissue typing across existing licensed conditions (thalassaemias, Diamond Blackfan Anaemia) were similar, and did not justify a case by case approach.
- There was concern about the time taken to reach a decision. Delays increase the anxiety of the family waiting for a decision, and risks to the existing child. The family can feel judged.

- The move to ELP consideration has shortened the licensing process, but that one month is still a significant delay.
- Case by case licensing can impact on the timing of a PCT decision to fund treatment – they will sometimes wait until the HFEA has granted a licence.
- More comprehensive patient information about the risks and benefits of transplant treatment from an HLA-matched sibling is needed. This should include information about time taken and cure rates of treatment.
- A minority thought that there are broader social implications and public concerns surrounding PTT, and oversight of each case by a regulator is required to maintain public confidence. Given the ethical concerns about PTT, it should always be a treatment of last resort.

4.15 It is important to note that the majority of delegates at the consultation event were PGD centre staff, all of whom shared a similar point of view about licensing. The minority who disagreed with the delegation of case by case decisions to PGD centre staff were concerned that about inappropriate use of the treatment, and held the view that independent regulation of tissue typing was essential.

#### *Summary of findings*

4.16 Based on the evidence gathered, it is clear that there are conditions (eg, Beta thalassaemia) for which donation of HLA matched tissue from a relative is the most effective option for treatment. Where a tissue matched relative is not available, PTT is thus the most appropriate option for each applicant case.

4.17 The case by case approach has been valuable insofar as it has allowed the opinion of consultant haematologists to be incorporated into the process. The view of these consultants is used to demonstrate that the proposed treatment is the most effective available, and that a tissue-matched sibling is the most effective available source of tissue. Evidence shows that the opinion of consultants about the appropriateness of treatment does not vary from case to case.

4.18 A further primary concern is the time taken to make a judgement, and the impact that this has on families

4.19 There needs to be reassurance that this treatment is independently regulated, ensuring that it is only used in appropriate cases.

#### *Analysis and policy alternatives*

4.20 In addressing the evidence, the committee needs to weigh up two perspectives:

- The need to maintain public confidence that these technologies are regulated by an independent body, and used appropriately by centres

- The need to sustain a robust licensing process which is in line with statutory requirements, but which does not place unnecessary burdens on centres and their patients.
- 4.21 Although the continued availability of PTT was supported by two-thirds majority in Parliament, there is a significant minority – both in Parliament and in society at large – who have real ethical concerns about this technique. Good regulatory oversight can, to some extent, respond to these concerns.
- 4.22 In approving the new process for licensing PGD, the Authority has retained rigorous oversight of novel diseases (where the testing for a disease is being done for the first time in the UK), whilst delegating the assessment of individual cases thereafter to the centres. The assessment of individual cases is done by reference to the criteria in the Code of Practice.
- 4.23 If the committee is minded, in the case of preimplantation tissue typing, to move towards licensing on a condition by condition basis, the Licence Committee would need to be satisfied, for applications for novel conditions, of the seriousness of the condition in general. This information could be provided by the relevant professional bodies, as could the suitability of the proposed treatment for a sick child. As the evidence shows, there are a number of conditions for which a transplantation of HLA-matched tissue will always be the most suitable treatment. For those conditions for which this is not the case, the committee could use its discretion to license on a case by case basis.
- 4.24 There may be some concern that guidance is not sufficiently forceful to ensure that centres offer PTT in appropriate cases. However, more rigorous oversight could be achieved through the addition of a licence condition requiring the following:
- That PGD centres carry out PTT only on the recommendation of the child's treating clinician, confirming the seriousness of the condition of the affected child, that this is effective treatment, and the most effective source of tissue.
  - That treatment only proceeds where the condition appears on the list of conditions approved as appropriately treated by a donation from a sibling born following PTT.
- 4.25 On the following page, three options have been set out for the future licensing of PTT, alongside the identified benefits and drawbacks of each.

| Options   | Benefits   | Drawbacks  |
|---|--|--|
| <p><b>1. Status quo: Continue to license applications on a case by case basis.</b> The Licence Committee would continue to be responsible for licensing novel conditions, and the ELP for subsequent applications for the same condition.</p>   | <p>Some streamlining of the process compared to previous LC scrutiny of each case</p> <p>Expertise of the child's clinician incorporated into the process and HFEA retains information about each case.</p> <p>Acknowledges concern about this technology, as expressed in Parliament.</p> | <p>Higher regulatory burden in comparison to licensing other forms of embryo testing.</p> <p>Does not completely address time concerns of stakeholders.</p>  |
| <p><b>2. License on a condition by condition basis.</b> The Licence Committee would continue to license novel conditions.</p> <p>PGD clinicians to decide on appropriateness of treatment for particular families using guidance in the Code of Practice and based on advice of child's treating clinician. Compliance to be checked on inspection.</p> | <p>Brings PTT into line with other forms of embryo testing.</p> <p>Expertise of the child's clinician still incorporated into the process.</p> <p>Maintains some public confidence that this technology is regulated through an inspection regime.</p>                                     | <p>May not adequately address concerns about PTT and the need for regulatory oversight.</p> <p>Code of Practice guidance not mandatory and therefore harder to enforce.</p> <p>'Bad practice' might not be detected.</p> |
| <p><b>3. Licence on a condition by condition basis.</b> The Licence Committee would continue to license novel conditions.</p> <p>PGD clinicians to decide on appropriateness of treatment for particular families based on advice of child's treating clinician, enforced through a licence condition. Compliance to be checked on inspection.</p>      | <p>Brings PTT into line with other forms of embryo testing.</p> <p>Expertise of the child's clinician incorporated into the process.</p> <p>Maintains some public confidence that this technology is regulated through an inspection regime based on mandatory requirements.</p>           | <p>May not adequately address concerns about PTT and the need for regulatory oversight</p>   |

**4.26 ELAC is asked to consider the alternative policy options, and provide a recommendation to the Authority on their preferred approach, alongside any caveats and/or modifications.**

**4.27 ELAC is also asked to agree that, in collaboration with the relevant professional bodies, the Executive develop more comprehensive patient information about tissue typing.**

*Next steps*

4.28 The next step is for a paper to be taken to the Authority on 20 January 2010 for decision. The recommendations of ELAC will be used to inform that paper.

## Annex A

**SCHEDULE 2**  
**ACTIVITIES FOR WHICH LICENCES MAY BE GRANTED**

*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,

(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,

(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, and

(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 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.

(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.

(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.

**Annex B****Application Form to carry out Preimplantation Genetic Diagnosis for Case-by Case Conditions or for Tissue Typing**

Please use this form to apply for preimplantation genetic diagnosis conditions (e.g. late on-set, lower penetrance and cancer susceptibility genes) and for human leukocyte antigen tissue typing (HLA) + / - preimplantation genetic diagnosis for a heritable genetic disease (PGD/HLA).

A separate form should be completed for each individual case.

It is important that the language used in this application is clear and understandable to non-specialist lay people. All abbreviations should be explained

Please submit the completed form to [pgd@hfea.gov.uk](mailto:pgd@hfea.gov.uk)

**1. Centre Details**

1.1 Person Responsible:

1.2 Centre name:

1.3 Centre number:

1.4 Genetic laboratory

Have details of the laboratory where genetic testing will be carried out, including details of the body that has accredited this laboratory, been submitted to the HFEA?

If no, please give details

**2. Patient Information**

2.1 Female patient:

2.2 Male patient:

### 3. Genetic Condition

3.1 Please provide details of the genetic condition for which preimplantation genetic diagnosis is proposed

Condition                      OMIM No (if appropriate)

3.2 Please provide a lay summary of the genetic condition / disorder (This summary should include a description of how the condition affects a person, how it is inherited and if, applicable any treatments for the condition) Note: This summary will be published on the HFEA website

3.3 Is purpose of testing the embryo to establish:

- a) whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth?
- b) whether it has a particular abnormality or any other gene, chromosome or mitochondrial abnormality?
- c) the sex of the embryo in 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?
  - iii. any other gender-related serious medical condition?

If yes to c) i, ii or iii – does the physical or mental disability, illness or other medical condition affect only one sex?

or it affects one significantly more than the other?

3.4 What is the risk of the embryo(s) having an abnormality?

3.4 Please provide information as to why, in your opinion, the genetic condition / disorder is a serious genetic condition/ disorder. In particular, you are asked to provide information on the following:

- age of onset;
- degree of penetrance;
- symptoms of the disease;
- variability of phenotype (i.e. mild to severe symptoms);
- whether the condition is treatable;

- type of treatment (if any, then the likely extent of treatment and its potential invasiveness);
- effect of the disease on quality of life (including speed of degeneration in progressive disorders and the extent of any physical and / or intellectual impairment)

- 3.5 Is there a significant risk that a person with the abnormality will have or will develop a serious physical or mental disability a serious illness or any other serious medical condition?

If yes, please provide your reasons

- 4.6 Is the centre going to carry out PGD as well as tissue typing?  
(HLA +/- PGD cases only)

## 5. Clinical decision-making (HLA +/- PGD cases only)

- 5.1 Is the proposed treatment supported by the clinician responsible for the care of the sibling child?

Please attach a copy of a letter from this clinician supporting this application

This letter should include information on:

- the degree of suffering associated with the disease of the affected sibling
- the speed of degeneration in progressive disorders
- the prognosis for the affected sibling in relation to all treatment options available?
- the availability of alternative sources of tissue for the treatment of the affected sibling, now and in the future
- the availability of effective therapy for the affected sibling, now and in the future

**Control sheet****Document control**

|                    |                                     |
|--------------------|-------------------------------------|
| Doc Name:          | Case by case decision making in PGD |
| TRIM ref/Doc No:   | 2009/08751                          |
| Latest Version No: | Version 1.3                         |
| Release date:      |                                     |
| Approved by:       |                                     |
| Next review due:   |                                     |
| Total pages:*      |                                     |

**Version/revision control**

| Version | Changes                        | Updated by:   | Release date |
|---------|--------------------------------|---------------|--------------|
| 1.1     | Juliet T                       | Danny Edwards |              |
| 1.2     | Juliet T, Charlotte A, Peter T | Danny Edwards |              |
| 1.3     | Juliet T, Charlotte A          | Danny Edwards |              |
|         |                                |               |              |

\* Excluding control sheet