Statutory Approvals Committee – minutes

Centre 0035 (Oxford Fertility)
Pre-implantation Genetic Diagnosis (PGD) application for Apert syndrome (acrocephalosyndactyly), OMIM #101200

Thursday, 31 January 2019

Church House, Dean's Yard, Westminster, London. SW1P 3NZ

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Emma Cave Ruth Wilde Rachel Cutting	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Sandrine Oakes Nicola Lawrence	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Inspector (Observer for Induction) Inspector (Observer for Induction)
Specialist Adviser	Dr Jenny Carmichael	
Legal Adviser	Tom Rider	Field Fisher LLP
Observers		

Declarations of interest

- Members of the committee declared that they had no conflicts of interest in relation to this item.

The committee had before it:

- 9th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members.

The following papers were considered by the committee:

- Executive Summary
- PGD Application Form
- Redacted Peer Review
- Genetic Alliance UK statement
- Licence Committee minutes, 11 November 1999, Approval of Crouzon Syndrome.
- SAC Minutes, 24 April 2014, PGD for Muenke Syndrome (OMIM #602849)
- Gene Reviews paper used by Executive: ‘FGFR related craniosynostosis syndromes’

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Jenny Carmichael who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for Apert syndrome, OMIM #101200 is consistent with the peer review.

1.3. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application.

1.4. The committee had regard to its decision tree. The committee noted that the centre is licensed to carry out PGD. The committee was also satisfied that the centre has experience of carrying out PGD and that generic patient information about its PGD programme and associated consent forms had previously been received by the HFEA.

1.5. The committee noted that the condition being applied for is not on the list of approved PGD conditions.

1.6. The committee noted that the proposed purpose of testing the embryos was as set out in paragraph 1ZA(1)(b) of Schedule 2 of the Act, i.e. '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'.

1.7. The committee noted that the condition is inherited in an autosomal dominant pattern which means there is a 50% chance of an embryo being affected with the condition in each pregnancy, if either parent has a relevant mutation. The penetrance of the condition is 100%, albeit there is variability in the severity of symptoms.

1.8. The committee noted that the condition is congenital and is characterised by early fusion of the bones in the skull so that the skull can't grow properly. The condition also affects the growth of bones in the face, leading to facial abnormalities and in some cases can result in breathing and feeding difficulties. Problems with skull growth can lead to neurological problems and approximately 50% of those affected have learning difficulties. Other problems include bone and skin syndactyly (fused fingers and toes) and abnormal joining of bones in the neck or back. The condition can be fatal if untreated and, if treated, by means of multiple surgical interventions cannot be cured and has a significant impact on quality of life.

1.9. The Peer Reviewer provided further information on the symptoms and their impact, notably that abnormal facial bone development can lead to upper airway obstruction in severe cases resulting, if untreated, in respiratory failure. In addition, abnormal skull development predisposes to raised intracranial pressure, with subsequent detrimental effects on brain development and cognitive function.

1.10. The committee noted that the Peer Reviewer identified that Apert syndrome, OMIM #101200, is one of eight FGFR (fibroblast growth factor receptor) related craniosynostosis syndromes, two of which are already licensed for PGD. The syndromes were named before the causative genes were identified, based on the particular pattern of synostosis and hand and feet abnormalities. Molecular advances have tied the conditions together - for example, the same genetic mutation has been identified in individuals with Crouzon, Pfeiffer and Jackson- Weiss syndromes. As more is learnt about the underlying genetic mechanisms, geneticists are now tending to consider these eight conditions as a group.

1.11. The Peer Reviewer suggested that as two of the eight FGFR related craniosynostosis syndromes are already licenced, the committee should consider licensing Pfeiffer syndrome (OMIM #101600), Jackson Weiss syndrome (OMIM #123150), Beare-Stevenson syndrome (OMIM #123790) and Crouzon syndrome with acanthocytosis nigricans (OMIM #612247), in addition to Apert syndrome (OMIM #101200).

1.12. The committee noted that the Executive investigated the eight conditions on the OMIM website and in a Gene Reviews publication, which was acknowledged in the papers. The conditions are listed in the table below, with the genes in which causative mutations have been characterised – all FGF receptor types. All the conditions are inherited in an autosomal dominant manner:

Syndrome (Licensing status)	**OMIM**	**Gene (OMIM) / inheritance**
Apert (No)	#101200	FGFR2 (*176943) / AD
Crouzon (Yes)	#123500	FGFR2 (*176943) / AD
Crouzon with acanthosis nigrans (No)	#612247	FGFR3 (*134934) / AD
Pfeiffer (No)	#101600	FGFR1 (*136350) / AD FGFR2 (*176943) / AD
Jackson Weiss (No)	#123150	FGFR1 (*136350) / AD FGFR2 (*176943) / AD
Beare Stevenson (No)	#123790	FGFR2 (*176943) / AD
Muenke (Yes)	#602849	FGFR3 (*134934) / AD
FGFR2-related isolated coronal synostosis (No)		FGFR2 (*176943) / AD

1.13. The committee acknowledged the minutes confirming that Crouzon syndrome, OMIM #123500, and Muenke syndrome, OMIM #602849, are already approved for PGD testing. It was also noted that one of the conditions, FGFR2-related isolated coronal synostosis, does not have an OMIM phenotype number and is not listed on the OMIM website, so therefore should not be considered for addition to the list of conditions for which PGD can be applied. The committee agreed that FGFR2-related isolated coronal synostosis should not be considered for PGD testing.

1.14. The committee welcomed the Specialist Advisor's advice that Crouzon with acanthosis nigrans syndrome, OMIM #612247; Pfeiffer syndrome, OMIM #101600; Jackson Weiss syndrome, OMIM #123150, and Beare Stevenson syndrome, OMIM #123790 all have similar clinical features to Apert syndrome, with comparable physical and neurological symptoms, alongside some learning disabilities, and confirming that they are all inherited in an autosomal dominant pattern.

1.15. The committee noted the inspectorate's request to consider whether Apert syndrome, OMIM #101200, should be considered for inclusion on the PGD List. The inspectorate also requested the committee considers Crouzon with acanthosis nigrans syndrome, OMIM #612247, Pfeiffer syndrome, OMIM #101600, Jackson Weiss syndrome, OMIM #123150, and Beare Stevenson syndrome, OMIM #123790, for inclusion on the PGD List. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Apert syndrome, OMIM #101200, is a serious condition, which is fully penetrant and present from birth, requiring extensive, repeated surgeries and can be life threatening. The condition can cause respiratory failure and a wide spectrum of physical and neurological symptoms. The condition may severely impact on the affected individual's quality of life.

2.2. The committee proceeded to consider the inspectorate's request to consider whether Crouzon with acanthosis nigrans syndrome, OMIM #612247, Pfeiffer syndrome, OMIM #101600, Jackson Weiss syndrome, OMIM #123150, and Beare Stevenson syndrome, OMIM #123790 should be added to the list of conditions for which PGD can be applied. The committee considered that in the worst case scenario, these are all serious conditions, in the same manner as Apert syndrome, OMIM #101200, which may have a severe impact on the individual, and may result in multiple physical and neurological disabilities.

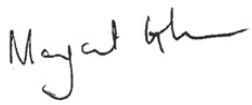
2.3. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing:

- Apert syndrome, OMIM #101200
- Crouzon with acanthosis nigrans syndrome, OMIM #612247
- Pfeiffer syndrome, OMIM #101600
- Jackson Weiss syndrome, OMIM #123150
- Beare Stevenson syndrome, OMIM #123790

3. Chairs signature

3.1. I confirm this is a true and accurate record of the meeting,

Signature



Name

Margaret Gilmore

Date

25 February 2019