Statutory Approvals Committee – minutes

Item 6

Centre 0044 (The Centre for Reproductive and Genetic Health)

Pre-implantation Genetic Diagnosis (PGD) application for Noonan Syndrome OMIM #610733

Thursday, 28 March 2019

HFEA Spey Meeting Room, Level 2, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Emma Cave Anne Lampe Tony Rutherford	
Members of the Executive	Moya Berry Catherine Burwood	Committee Secretary Licensing Manager (Observer)
Specialist Adviser	Dr Alison Male (PGD)	
Legal Adviser	Tom Rider	Fieldfisher LLP
Observers	Hannah Carpenter	Policy Officer

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
- LC minutes 26 April 2012 – PGD for Noonan Syndrome Type 1, OMIM # 163950

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Dr Alison Male, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the PGD application for Noonan Syndrome Type 4, OMIM #610733, was consistent with the peer review.

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

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

1.5. 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.

1.6. 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 Noonan Syndrome Type 4 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.

1.8. Noonan Syndrome Type 4 has variable expressivity as shown by the range and varying frequency of symptoms. The exact penetrance is not known but is close to 100%.

1.9. The condition is characterised by short stature, congenital heart disease and characteristic facial features. Other features of the condition include renal abnormalities, a short/webbed neck, abnormal chest shape and undescended testes, coagulation defects, lymphatic abnormalities, eye abnormalities, and hearing impairment. Some patients develop cardiomyopathy, which can develop in infancy, childhood or adulthood.

1.10. Cardiovascular abnormalities are seen in 50 - 80% of cases of Noonan Syndrome and include heart defects such as pulmonary valve stenosis, hypertrophic cardiomyopathy and septal wall defects, and vascular defects, such as branch pulmonary artery stenosis and coarctation of the aorta. Intellectual impairment is very variable from mild to severe. There is an increased risk of leukaemia and other cancers.

1.11. There is no cure for Noonan Syndrome Type 4, and management depends on the presenting features, which may require surgery. Noonan Syndrome Type 4 can impact on life expectancy depending on the severity of cardiovascular defects and the success of treatment interventions, some of which are not themselves without risk to life.

1.12. The committee noted the inspectorate's request to consider whether Noonan Syndrome Type 4, OMIM #610733 should be approved for inclusion on the list of conditions approved for PGD. The committee agreed to consider the application on this basis.

1.13. The committee also noted that Noonan Syndrome can be caused by a mutation in a number of genes and that it is rarely possible to clinically differentiate between different types of Noonan Syndrome. The committee noted the recommendation of the peer reviewer to consider all the other currently unlicensed Noonan Syndrome types (types 2, 3, 5, 6, 7, 8, 9 and 10) for approval as conditions for which PGD can be applied. The risk of inheriting Noonan Syndrome types 3,5,6,7,8,9.and 10 is 50% if either parent carries a relevant mutation. For Noonan Syndrome type 2, the risk of inheritance is 25% if each parent has a relevant mutation. The penetrance is thought to be 100%. All conditions are associated with short stature, heart and

vascular defects, developmental delay, intellectual disability, short webbed neck and characteristic facial features.

2. Decision

2.1. The committee considered that, in the worst-case scenario Noonan Syndrome Type 4, OMIM #610733 is a serious multi-faceted condition that can be fatal. There is an increased risk of childhood cancers. Some patients develop hypertrophic cardiomyopathy which can occur in infancy, childhood or adulthood and may be associated with early mortality. Other features include renal abnormalities, coagulation defects, lymphatic abnormalities, eye abnormalities and hearing impairment. There is no cure for the condition which can have a significant effect on the quality of life, with an increased risk of depression/ anxiety for some patients.

2.2. The committee considered the recommendation that Noonan Syndrome types (types 2,3,5, 6, 7, 8, 9 and 10) are also added to the list of conditions for which PGD can be applied. The committee noted the advice of the specialist adviser and agreed that the clinical features for the above conditions are within the clinical spectrum of Noonan syndrome, and in the worst-case scenario are the same as those for Noonan Syndrome Type 4.

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, that a person with the abnormality will, given the conditions' worst symptoms, have or develop a serious physical disability, a serious illness or any other serious medical condition.

2.4. The committee was therefore satisfied that the following conditions the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing for.

- Noonan Syndrome type 4, OMIM #610733

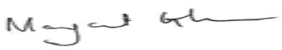
The committee also agreed to test the following conditions:

- Noonan Syndrome type 2, OMIM #605275
- Noonan Syndrome type 3, OMIM #609942
- Noonan Syndrome type 5, OMIM #611553
- Noonan Syndrome type 6, OMIM #613224
- Noonan Syndrome type 7, OMIM #613706
- Noonan Syndrome type 8, OMIM #615355
- Noonan Syndrome type 9, OMIM #616559
- Noonan Syndrome type 10, OMIM #616564

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

24 April 2019