Statutory Approvals Committee – minutes

Item 3

Centre 0119 (Birmingham Women's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for

Cancer susceptibility due to mutation in Partner and Localizer of BRCA2 (PALB2), OMIM *610355

Thursday, 29 November 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Anthony Rutherford Ruth Wilde Emma Cave	
Members of the Executive	Catherine Burwood Dee Knoyle Paula Robinson Victoria Askew	Senior Governance Manager (Secretary) Committee Secretary (Observer) Head of Planning and Governance (Observer) Inspections & Logistics Officer (Observer)
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Ros Foster	Browne Jacobson LLP
Observers	Rachel Cutting (New Member induction - observer)	

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:

- 8th 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
- 13-02-2008 LC minutes for PGD, BRCA1 OMIM *113705
- 24-06-2010 LC minutes for PGD, BRCA2 OMIM *600185 and #612555
- ‘A beginner’s guide to BRCA1 and BRCA2, Royal Marsden NHS Foundation Trust.
- 24-07-2008 LC minutes for PGD/HLA for Fanconi Anaemia A
- 24-07-2008 LC minutes for PGD/HLA for Fanconi Anaemia C

1. Consideration of application

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

1.2. The committee noted that the description in the application for PGD cancer susceptibility due to mutation in Partner and Localizer of BRCA2 (PALB2), OMIM *610355 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 cancer susceptibility due to mutation in PALB2, OMIM *610355 is inherited in an autosomal dominant pattern which means there is a 50% chance that an embryo would inherit the condition in each pregnancy, if either parent has a relevant mutation.

1.8. The committee noted Licence Committee approvals for other such genes e.g. BRCA1, OMIM *113705 and BRCA2, OMIM *600185 and #612555.

1.9. In considering the application for cancer susceptibility due to mutation in Partner and Localizer of BRCA2 (PALB2), OMIM *610355 the committee noted that the risk of inheriting the condition is 50% in each pregnancy if either parent carries a causative mutation. 30-60% of female carriers of the mutation will develop breast cancer before the age of 70 years. The risk for ovarian cancer is unknown at present but there appears to be a small increase in the risk of developing pancreatic cancer and of breast cancer in males. BRCA1 and BRCA2 gene mutations are already approved for PGD and these increase breast cancer susceptibility through a similar mechanism to PALB2. Minutes of the approvals were in the committee papers, along with a patient guide to BRCA1 and BRCA2 produced by the Royal Marsden NHS Foundation Trust. This latter document states that the risk of breast cancer in women before the age of 80 years, is 60-90% for BRCA1 mutation and 45-85% for BRCA2 mutation. BRCA1 and BRCA2 also pre-dispose to ovarian cancer.

1.10. The committee also noted that compound heterozygous or homozygous (biallelic) mutations in PALB2 cause the condition Fanconi Anaemia type N, OMIM #610832. The avoidance of this condition can be considered an additional purpose of PGD involving PALB2 mutation testing if it is known that both partners have heterozygous PALB2 mutations.

1.11. The committee noted that Fanconi Anaemia type N, OMIM #610832 due to mutations in PALB2 is inherited in an autosomal recessive manner which means there is 25% chance of having an affected child in each pregnancy, if both parents have a relevant PALB2 mutation.

1.12. Fanconi Anaemia type N, OMIM #610832 has a penetrance of 100%. The condition is a severe form of Fanconi Anaemia which is associated with congenital abnormalities, early bone marrow

failure and a near 100% risk of leukaemia and solid tumours under the age of 10. The committee noted that Fanconi Anaemia types A, OMIM #607139 and C, OMIM #227645 are already approved for PGD. Minutes of the approvals were in the committee papers.

1.13. The committee noted that the underlying disease processes related to PALB2 mutation are untreatable. Females with heterozygous mutations in PALB2 have approximately a 30-60% chance of developing breast cancer over their lifetime, against a risk of 12% in those without the mutation. There also appears to be a small increase in risk of developing pancreatic cancer and breast cancer in males. Cancers may be treated, but treatment is not always successful and early death may result. Nearly 40% of the breast cancers that develop are "triple negative" (compared to 12-24% of all breast cancers) and carry a poorer prognosis than other types of breast cancer. Risk reducing surgery is an option. Where cancers do not develop, there is no direct impact on quality of life but the risk of cancer causes prolonged anxiety, as well as the inconvenience of additional surveillance and, if risk reducing surgery is used, the possibility of complications related to the surgery. Individuals with homozygous or compound heterozygous mutations in PALB2 will have Fanconi Anaemia type N and have a severely impaired quality of life as a result of being born with congenital abnormalities and having a near 100% chance of developing a childhood cancer, which may be untreatable. Further tumours may occur in different locations. Life expectancy will be severely curtailed, and the child would be very unlikely to reach teenage years.

1.14. The committee noted the inspectorate's request to consider whether the primary condition in the application for cancer susceptibility due to mutation in Partner and Localizer of BRCA2 (PALB2), OMIM *610355 should be approved for inclusion on the PGD List. The inspectorate also requested the committee consider approving the secondary condition for Fanconi Anaemia type N, OMIM #610832. The committee agreed to consider the application.

2. Decision

2.1. The committee considered that, in the worst case scenario, cancer susceptibility due to mutation in Partner and Localizer of BRCA2 (PALB2), OMIM *610355, is a serious condition, which can lead to aggressive and life-threatening forms of cancer. Sufferers may live with anxiety in the knowledge that they are at an increased risk of developing cancers which may impact quality of life.

2.2. The committee proceeded to consider the inspectorate's request to consider whether Fanconi Anaemia type N (OMIM #610832) should be added to the list of conditions for which PGD can be applied. The committee considered that Fanconi Anaemia type N, OMIM #610832 is, in the worst case scenario, a serious condition which will lead to the development of early onset cancer and likely death in childhood. Quality of life for sufferers may be impaired due to being born with congenital abnormalities.

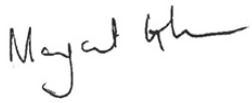
2.3. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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:

- Partner and Localizer of BRCA2 (PALB2), OMIM *610355
- Fanconi Anaemia type N, OMIM #610832.

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

19 December 2018