Statutory Approvals Committee – minutes

Item 6

Centre 0102 (Guys Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for Emberger Syndrome OMIM #614038

Thursday, 28 February 2019

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

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Ruth Wilde Rachel Cutting Emma Cave	
Members of the Executive	Moya Berry Dee Knoyle Catherine Burwood	Committee Secretary Committee Secretary (Observer) Senior Governance Manager (Observer)
Legal Adviser	Sarah Ellson	Fieldfisher LLP
External adviser	Dr Alan Fryer	
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
- Statutory Approvals Committee Minutes -25 August 2016, PGD for Familial Myelodysplastic Syndrome
- Statutory Approvals Committee Minutes 13 December 2018, PGD for Immunodeficiency 44

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 Hereditary Emberger Syndrome, OMIM #614038, was consistent with the peer review.

1.3. The committee noted that the conditions being applied for are 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 Emberger Syndrome 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.

1.8. The committee noted there was insufficient information to accurately predict the penetrance of Emberger Syndrome. Lymphoedema and haematological abnormalities are known to be highly penetrant in reported families. Other associated features such as deafness have reduced penetrance.

1.9. The committee noted that Emberger Syndrome is a description of a group of specific clinical features found in a subset of patients who carry a mutation in the GATA2 gene. The specific features of Emberger syndrome are primary lymphoedema (swelling) of the lower extremities and external genitalia and haematological abnormalities such as pancytopenia (deficiency of all three cellular components of the blood - red cells, white cells, and platelets), myelodysplasia (bone marrow dysfunction) and Acute Myeloblastic Leukaemia (blood cancer). Other features include deafness and facial dysmorphism.

1.10. Lymphoedema in patients with Emberger Syndrome can be marked, leading to very swollen and disfigured legs, and may develop at any time from early infancy up to puberty. Patients can experience an increased susceptibility to infections and also blood disorders including leukaemia. Deafness, when present, is congenital and severe. Facial dysmorphism involves abnormalities such as webbed neck, and prominent eyelid folds.

1.11. There is no cure for Emberger Syndrome, so treatments focus on the management of symptoms and complications as they arise. Stem cell transplantation for the haematological disorders is not always successful. The condition is potentially life threatening and may severely affect the patient’s quality of life.

1.12. The committee noted that Emberger Syndrome is one of a group of disorders caused by GATA2 mutations and noted the recommendation of the peer reviewer to consider several

other conditions caused by GATA2 mutations for approval as conditions for which PGD can be applied.

1.13. Thus, the review also includes the conditions; Immunodeficiency 21, OMIM #614172, which is related to GATA2 mutation, Leukaemia acute myeloid, OMIM 601626 and Myelodysplastic Syndrome, OMIM #614286.

1.14. The committee noted that Myelodysplastic Syndrome, OMIM #614286, is already approved for PGD.

1.15. The committee noted the views of the executive regarding the peer reviewer's proposal to include Leukaemia, acute myeloid, OMIM #601626 within the application. Multiple (22) genes are listed on the OMIM website entry for #601426 as having a role in the condition, but only the six genes listed in the table below have an apparent causative role, i.e. considered to have a clear inherited genotype-phenotype correlation. For the other genes that relationship is not clear - their 'proven' role in some cases is via a somatic mutation rather than an inherited mutation or they are implicated as a component of a fusion protein. In addition, as is the nature of cancer genetics, 'causative' gene mutations are rarely 100% penetrant but function as susceptibility factors. The correlation between the gene mutations listed in Table 1 and the incidence of Leukaemia, acute myeloid, OMIM #601626, is not provided by the peer reviewer – except for the statement that 20% of those affected by GATA2 mutations will develop acute myeloid leukaemia. There was no other relevant information regarding the other gene mutations listed in the table below.

Gene	Gene OMIM *	Inheritance pattern	Aetiology
GATA2	137295	AD, SMu	Mutation
KIT	164920	AD, SMu	Mutation
TERT	187270	AD, SMu	Mutation
KRAS	190070	AD, SMu	Mutation
CEBPA	116897	AD, SMu	Mutation
RUNX1	151385	AD, SMu	Mutation

1.16. In the worst-case scenario, mutations in the genes in the table can cause fatal acute myeloid leukaemia. 20% of those affected by GATA2 mutations will develop acute myeloid leukaemia However, the actual age-risk profile for Leukaemia, acute myeloid, OMIM #601626, in those carrying mutations in the genes listed in the table is not available.

1.17. Given the peer reviewer's statement that 20% of those affected by GATA2 mutations will develop acute myeloid leukaemia, the committee received and accepted the advice from the Specialist Adviser who confirmed the following conditions: Immunodeficiency 21, OMIM #614172 and Leukaemia, acute myeloid, OMIM #601626, related to GATA2 mutation, should be the conditions for which PGD can be applied.

2. Decision

2.1. The committee considered that, in the worst-case scenario, Hereditary Emberger Syndrome OMIM #61403 is a serious condition given its early onset, lifelong risk of developing cancer and early death and severe effect on the quality of life. Patients can experience an increased susceptibility to blood disorders including leukaemia from as early as infancy and are also at risk from infections. Lymphoedema in patients with Emberger Syndrome can be marked, leading to very swollen and disfigured legs. Other features include deafness and facial dysmorphism. There is no cure for the condition.

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2.2. The committee considered the recommendation that Immunodeficiency 21, OMIM #614172 and Leukaemia, acute myeloid, OMIM #601626, related to GATA2 mutation, are also added to the list of conditions for which PGD can be applied. The committee noted that the risk of inheriting Immunodeficiency 21 is 50% in each pregnancy if either parent carries a causative mutation. Immunodeficiency 21 causes similar haematological and immunological abnormalities as seen in Emberger syndrome and in the worst-case scenario, death through overwhelming infection or the complications of myeloid leukaemia are possible. With regard to Leukaemia, acute myeloid, related to GATA2 mutation, 20% of those affected by GATA2 mutations will develop acute myeloid leukaemia and in the worst-case scenario the condition may be fatal.

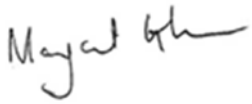
2.3. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the conditions' worst symptoms, that a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

- Hereditary Emberger Syndrome, OMIM #614038
- Immunodeficiency 21, OMIM #614172
- Leukaemia, acute myeloid, OMIM #601626, related to GATA2 mutation

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

14 March 2019