Statutory Approvals Committee – minutes

Centre 0314 (Leeds Fertility)

Pre-implantation Genetic Diagnosis (PGD) application for Diarrhea 2, with Microvillus Atrophy (DIAR2) OMIM #251850 also known as Microvillus Inclusion Disease

Thursday, 27 February 2020

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

Committee members	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde	
Members of the Executive	Moya Berry Catherine Burwood	Committee Officer Licensing Manager
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Tom Rider	FieldFisher - LLP
Observer	Emily Tiemann (Induction)	Policy Officer

Declarations of interest

- Tony Rutherford declared an interest with this item and withdrew from discussion during this part of the meeting.
- There were no other conflicts of interest declared by any other members of the committee.

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

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 PGD application for Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850, is 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 Diarrhea 2, with Microvillus Atrophy (DIAR2) is also known as Microvillus Inclusion Disease. To ensure consistency with the OMIM website, the condition for the purposes of this application, will be known as Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850.

1.5. The committee noted that the Genetic Alliance UK statement provided a perspective on the impact of the condition on patients, their families and carers.

1.6. 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.

1.7. 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'.

1.8. The committee noted Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850, is inherited in an autosomal recessive pattern, which means there is a 25% chance of an embryo being affected by the condition in each pregnancy if each parent has a relevant mutation.

1.9. The committee noted the penetrance of the condition is 100%.

1.10. Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850 is a rare genetic disease of the intestine that presents at birth or within the first months of life. The condition causes severe diarrhoea and an inability to absorb nutrients. The prognosis of those affected is very poor and many children die within the first three years of life.

1.11. There is no cure for this condition and treatment focuses on managing the symptoms.

1.12. The committee noted the executive's request to consider Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850, for inclusion on the list of conditions approved for PGD. The committee agreed to consider the application on this basis. The committee noted that the OMIM entry 251850 refers to the condition being caused by mutations in the MYOB5 gene but that the applicant and peer reviewer indicated that a clinically similar condition is also caused by mutations in the STX3 gene. The specialist adviser also reported that mutations in another gene STXBP2 are also a recognised cause of the phenotype and this gene is associated with a condition that has already been licensed for PGD by the HFEA (OMIM 613101).

1.13. The committee noted the recommendation of the executive to consider a number of additional conditions for inclusion on the list of conditions approved for PGD. The peer reviewer considers there is reasonable evidence that the following conditions have a similar phenotype to DIAR2. The conditions are inherited in an autosomal recessive manner and their penetrance is thought to be 100%. All the conditions present at birth or within the early postnatal period and are characterised by severe diarrhoea, which causes fluid imbalance, dehydration and an inability to absorb nutrients, with the same results, complications and risks to life as DIAR2. The prognosis of those affected can be very poor and death in childhood is possible in each of the conditions. The conditions are:

- Diarrhea 1, secretory chloride congenital, (DIAR1), OMIM #214700
- Diarrhea 3, secretory sodium, congenital syndromic (DIAR3), OMIM #270420

- Diarrhea 5, with tufting enteropathy, congenital, (DIAR5), OMIM #613217
- Diarrhea 8, secretory sodium, congenital, (DIAR8), OMIM #616868
- Diarrhea 10, protein losing enteropathy, type, (DIAR10), OMIM #618183
- Diarrhea 11, malabsorptive, congenital, (DIAR11), OMIM #618662

1.14. The committee noted the executive's recommendation, based on the advice of the peer reviewer, not to include the following conditions on the list for which PGD can be applied as gene assignments are thus far based on a very small number of families affected with the conditions. These conditions are Diarrhea 4, (DIAR4), OMIM #610370, Diarrhea 6, (DIAR6), OMIM #614616 Diarrhea 7, (DIAR7), OMIM #615863 and Diarrhea 9, (DIAR9), OMIM #618168.

2. Decision

2.1. The committee considered that, in the worst-case scenario Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850, is a rare, serious and often lethal condition which presents at birth or within the first three months of life and can cause a high degree of suffering. There is no cure for the condition and the committee noted that some treatments are considered to be very high-risk, including long-term total parenteral nutrition with the risk of infection and liver damage and small bowel transplantation. Cholestatic liver disease was also noted to be a complication which might require liver transplantation. The committee considered the possible adverse implications and impact on the quality of life for those affected with the condition.

2.2. The committee considered in the worst-case scenario the following conditions that present similarly and which have (in the cases of Diarrhea 3, 5,10 and 11) similar treatment options and poor prognosis:

- Diarrhea 1, Secretory Chloride, Congenital, (DIAR1), OMIM #214700
- Diarrhea 3, Secretory Sodium, Congenital Syndromic (DIAR3), OMIM #270420
- Diarrhea 5, with Tufting Enteropathy, Congenital, (DIAR5), OMIM #613217
- Diarrhea 8, Secretory Sodium, Congenital, (DIAR8), OMIM #616868
- Diarrhea 10, Protein Losing Enteropathy, type, (DIAR10), OMIM #618183
- Diarrhea 11, Malabsorptive, Congenital, (DIAR11), OMIM #618662

Diarrhea 3 was also noted to be associated with congenital abnormalities such as choanal and intestinal atresias and a keratopathy. Diarrhea 1 and 8 are usually fatal in infancy if not diagnosed and treated appropriately, though afterwards can be managed with life-long oral fluid and mineral replacement. These surviving children have persistent diarrhoea and remain at risk of life-threatening fluid losses in the event of acute infections and can develop other complications such as inflammatory bowel disease and renal impairment. In the worst-case scenario, the quality of life of these children and adults is severely impacted and the condition may result in early death.

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 abnormalities in question and that there is a significant risk that a person with such an 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 meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act. The committee agreed to authorise testing for:

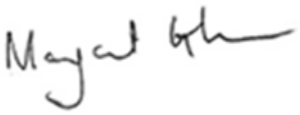
- Diarrhea 1, Secretory Chloride, Congenital, (DIAR1), OMIM #214700
- Diarrhea 2, with Microvillus Atrophy (DIAR2), OMIM #251850
- Diarrhea 3, Secretory Sodium, Congenital Syndromic (DIAR3), OMIM #270420
- Diarrhea 5, with Tufting Enteropathy, Congenital, (DIAR5), OMIM #613217
- Diarrhea 8, Secretory Sodium, Congenital, (DIAR8), OMIM #616868
- Diarrhea 10, Protein Losing Enteropathy, type, (DIAR10), OMIM #618183
- Diarrhea 11, Malabsorptive, Congenital, (DIAR11), OMIM #618662

2.5. With regard to Diarrhea 4, (DIAR4), OMIM #610370, Diarrhea 6, (DIAR6), OMIM #614616 Diarrhea 7, (DIAR7), OMIM #615863 and Diarrhea 9, (DIAR9), OMIM #618168, the committee considered the advice of its specialist adviser, and agreed that these conditions should not be considered for PGD at this time.

3. Chairs signature

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

Signature



Name
Margaret Gilmore

Date
17 March 2020