Statutory Approvals Committee - minutes

Centre 0005 (Fertility Exeter)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) application for Myopathic Ehlers-Danlos Syndrome (mEDS) / Bethlem myopathy-2 (BTHLM2), OMIM #616471

Date:	29 July 2021
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde
Specialist Adviser:	Professor Peter Turnpenny
Legal Adviser:	Sarah Ellson – FieldFisher LLP
Members of the Executive:	Dee Knoyle - Committee Officer (Secretary) Moya Berry - Committee Officer (observer) Catherine Burwood – Licensing Manager (observer)
Observers:	Jonathan Herring – HFEA Authority Member
Declarations of Interest:	Members of the committee declared that they had no conflicts of interest in relation to this item. Peter Turnpenny declared that he works at consultant clinics on a contract basis with the Royal Devon & Exeter Hospital. He has not been involved with this application.

The Committee had before it:

- 9th edition
- Standard Licencing and Approvals Pack

The following papers were considered by the committee:

- Executive Summary
- PGT-M Application form
- Redacted Peer review
- Genetic Alliance Statement

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Professor Peter Turnpenny, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the PGT-M application for Myopathic Ehlers-Danlos syndrome (mEDS) / Bethlem myopathy-2 (BTHLM2), OMIM #616471 is consistent with the peer review.

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

1.4. The committee noted that the condition is known as is Bethlem Myopathy 2 (BTHLM2), OMIM #616471 on the OMIM website. To ensure consistency the condition will be known as Bethlem Myopathy 2 (BTHLM2), OMIM #616471.

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 application form states that centre 0005 is licensed to perform embryo testing, however this is not the case. The Person Responsible has confirmed that this was an error when completing the form and that the centre that will perform the embryo biopsy, if this application is approved, is Guys Hospital, centre 0102, which is licensed to perform embryo testing. The executive understands that it is acceptable for centres which are not licensed for embryo testing to make applications for a condition to be approved for PGT-M by the HFEA.

1.7. Generic patient information about the PGT-M programme at centre 0102 and associated consent forms have previously been submitted to the HFEA and were considered to be compliant with HFEA requirements.

1.8. 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'.

1.9. The committee noted that Bethlem Myopathy 2 (BTHLM2), OMIM #616471, is inherited in an autosomal dominant manner, which means there is a 50% chance of an embryo being affected by the condition in each pregnancy if either parent has a relevant mutation. BTHLM2 is caused by heterozygous mutation in the COL12A1 gene. The specialist adviser confirmed that the condition can also occur de novo. There is an autosomal recessive condition caused by two alterations in COL12A1 (OMIM #616470) which, according to the limited medical literature, is much more severe.

1.10. The committee noted that the penetrance of the condition is likely to be high, but with very variable expression.

1.11. The onset of symptoms for BTHLM2 is usually in infancy or early childhood; in some individuals the condition may progress slowly in adulthood with increasing weakness. The condition is characterised by hypotonia in infancy (floppiness and poor muscle tone) that usually improves, delayed motor milestones (e.g. holding head up, sitting unaided and walking), joint hypermobility of small and large joints, joint dislocations and also contractures of large joints, including hips, knees and elbows, which could affect mobility. This could lead to significant

disability in later life for some people, however in most individuals it is mild. There can be poor wound healing, leading to atrophic scars which are depressed in appearance.

1.12. The committee noted that some individuals with the COL12A1 mutation may develop scoliosis or kyphosis (forms of abnormal spinal curvature). Heart and lung manifestations are not seen, in contrast to many other myopathies. Intellectual disability is not a feature of the condition.

1.13. There are no treatments available to cure this disease.

1.14. The committee noted the peer reviewer's comments.

1.15. The committee noted that individuals with significant muscle weakness will require regular assessments with physiotherapy, neuromuscular specialists, occupational therapy, possible speech and language therapy. In the most severe cases they may require echocardiology and respiratory assessments. As this is a new condition with less than 20 reported cases the natural history is not well studied. Initially some children who are quite weak can show some improvement, however some adults who present later may have gradual progressive weakness. In Bethlem myopathy type 1 there can often be a deterioration in later adult life resulting in respiratory failure and dependance on non-invasive ventilatory support. The peer reviewer was unable to find reports of this for Bethlem type 2.

1.16. The committee noted the executive's request to consider Bethlem Myopathy 2 (BTHLM2), OMIM #616471, for inclusion on the list of conditions approved for PGT-M. The committee noted that if the application is approved, the conditions will be published on the HFEA website, and all centres licensed to conduct PGT-M will be able to perform PGT-M to screen for the conditions. The committee agreed to consider the application on this basis.

1.17. The committee noted that BTHLM2 has clinical similarities with Bethlem Myopathy, OMIM #158810, which is already approved for PGT-M and is listed on the HFEA website. The committee noted the executive's request to consider whether the name should be changed on the HFEA website to Bethlem Myopathy 1 (BTHLM1) for accuracy.

2. Decision

2.1. The committee agreed that the condition Bethlem Myopathy, OMIM #158810, which has already been approved for PGT-M and listed on the HFEA website, should be renamed Bethlem Myopathy 1 (BTHLM1) for accuracy.

2.2. The committee reviewed the application and guidance provided by its Specialist Adviser and, after careful consideration, decided to adjourn its decision to authorise testing for Bethlem Myopathy 2 (BTHLM2), OMIM #616471.

2.3. The committee requested further information on how Bethlem Myopathy 2 (BTHLM2), OMIM #616471 has affected this particular family. Information should include, but is not limited to, the following:

- How many people in the immediate family or relatives have BTHLM2 and what was the age of onset, including information on whether the condition is progressive for them.
- How has BTHLM2 affected these individuals, e.g. type and severity of dislocations and contractures, kyphosis or scoliosis, muscle weakness, wound healing issues, and history of scaring. Also provide information on the degree of pain associated with this condition and any hospitalisation or hospital visits for treatment, and whether any surgeries were involved. Were there any serious complications associated with this condition at any stage for these individuals i.e. cardiac or respiratory complications?

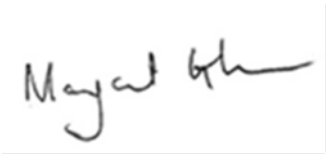
- Information on mobility assistance required e.g. walking aids, regular essential therapy.

2.4. The committee agreed to resume its consideration of this application when further information is provided.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

19 August 2021