Statutory Approvals Committee – minutes

Centre 0102 (Guys Hospital)
Pre-implantation Genetic Diagnosis (PGD) application for Thiamine-responsive Megaloblastic Anaemia, OMIM #249270

Thursday, 27 September 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Ruth Wilde	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Specialist Adviser	Professor Peter Turnpenny	
Legal Adviser	Dawn Brathwaite	Mills & Reeve LLP
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:

- 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
- Email from centre confirming application for 11 LCCS types
- Genetic Alliance UK 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 application for PGD for Thiamine-responsive Megaloblastic Anaemia, OMIM #249270, 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 the condition is inherited in an autosomal recessive pattern which means there is a 25% chance of an embryo being affected with the condition in each pregnancy, if both parents have a relevant mutation.

1.8. The committee noted that Thiamine-responsive Megaloblastic Anaemia is caused by homozygous mutations in the *SLC19A2* gene, which encodes a thiamine transporter protein. The condition is characterised by hearing loss, diabetes and a blood disorder called megaloblastic anaemia, in which a person has a low number of red blood cells (anaemia), many of which are larger than normal (megaloblastic). Age of onset is between infancy and adolescence.

1.9. The symptoms of the condition are hearing loss, diabetes (which usually requires insulin) decreased appetite, lack of energy, headaches, pale skin, diarrhoea and tingling or numbness in the hands and feet. Other symptoms include eye problems (optic atrophy), heart rhythm abnormalities such as atrial tachycardia, heart structural abnormalities such as atrial septal defects and ventricular septal defects, and neurological abnormalities such as stroke and epilepsy. The main triad of clinical features - the megaloblastic anaemia, hearing loss and diabetes – are seen in virtually all patients but the other symptoms will vary from individual to individual. The condition is 100% penetrant in those children inheriting a faulty copy of the gene from both parents.

1.10. Treatment for this condition is lifelong use of pharmacologic doses (50-100mg/day) of oral thiamine. This improves the anaemia, but if medication is stopped, the anaemia will return. Red blood cell transfusion may be needed for severe anaemia. Progressive sensorineural hearing loss is irreversible and may not be prevented by thiamine treatment. Some children have required cochlear implants. Insulin is generally needed for the diabetes, however in some cases the thiamine supplements may reduce the insulin requirements. Thiamine treatment has not been evaluated for its impact on optic atrophy and the cardiovascular and neurological abnormalities.

1.11. The condition has significant impact on quality of life as children with the condition require yearly monitoring with blood tests, hearing tests, assessment for glucose intolerance, and ophthalmological, cardiac and neurological evaluation. They will need audiology support, speech and language therapy and additional support at school. They may require other input depending on their ophthalmological, cardiac and neurological condition. Treatment with thiamine is sometimes not successful, so anaemia, hearing loss, diabetes, and eye, heart and neurological defects will impact on some of those living with the condition to varying degrees.

1.12. The committee noted that Thiamine-responsive Megaloblastic Anaemia, OMIM #249270, is also known as Thiamine Metabolism Dysfunction Syndrome (THMD) type 1. The Peer Reviewer recommended that THMD types 2- 5 are also considered for approval as conditions for which PGD can be applied, because they have the same pattern of inheritance and, on worst case scenario, severe outcome with unpredictable response to treatment - even though they are rather different in clinical presentation, the neurological symptoms predominating.

1.13. The committee noted the table below, prepared by the Executive, providing information from the OMIM website and in the peer review, presenting the genetic etiology and common symptoms in THMD types 2-5, for the committee's information:

Condition	**Causative gene (OMIM number) / Inheritance pattern[1]**	**Description in the worst case**
THMD2 OMIM #607483	SLC19A3 (*606152) Autosomal recessive	Presents as an episodic encephalopathy, with confusion, seizures and sometimes coma and death, that can be triggered by febrile illnesses. Treatment with biotin or sometimes thiamine can result in partial or complete improvement but, if untreated, can lead to a permanent dystonia.
THMD3 OMIM #607196	SLC25A19 (*606521) Autosomal recessive	Presents with severe congenital microcephaly from birth and profound developmental retardation and may be fatal in early childhood.
THMD4 OMIM #613710	SLC25A19 (*606521) Autosomal recessive	THMD4 is similar to THMD2 - most patients recover fully from acute episodes but may develop a chronic axonal polyneuropathy.
THMD5 OMIM #614458	TPK1 (*606370) Autosomal recessive	Typically presents with episodes of encephalopathy that can lead to progressive neurological dysfunction which can result in the loss of ability to walk. Cognitive function is usually preserved.

1.14. The committee welcomed the advice of the Specialist Adviser, who clarified that THMD3 is a severe disorder, which can be more debilitating than Thiamine-responsive Megaloblastic Anaemia, OMIM #249270, the condition formulating the centre's primary application. THMD5 is also a severe disorder and resistant to treatment. The Specialist Adviser informed the committee that THMD2 can be severe early in life, but can respond well with thiamine and biotin; untreated the condition can be very serious. THMD4 is caused by the same gene as THMD3, but is a milder condition and affected individuals can lead a relatively normal life. In the worst case scenario, THMD4 can impact on motor and sensory abilities, and in rare cases can be disabling.

1.15. The committee noted the inspectorate's request to consider whether Thiamine-responsive Megaloblastic Anaemia, OMIM #249270 should be approved for inclusion on the PGD List. The inspectorate also requested the committee consider approving the additional forms of Thiamine Metabolism Dysfunction Syndrome (types 2-5) suggested by the Peer Reviewer as these conditions have the same pattern on inheritance, are close to 100% penetrant, can, in the worst case scenario, each lead to significant neurological impairment impacting on quality of life, e.g. dystonia, loss of the ability to walk, or, in the case of THMD2 and 3, death. Thiamine treatment may provide some relief in THMD2 if the condition is diagnosed. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario Thiamine-responsive Megaloblastic Anaemia, OMIM #249270 is serious given the multi-system nature of the condition, it's early onset, its neurological impact and cumulative effect. Cardiovascular complications can occur, including sudden death, stroke, heart failure, heart rhythm disorders and congenital heart defects. Treatment does not eradicate all symptoms. The condition severely impacts on the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to approve the THMD types 2-5 noting the advice of the Specialist Adviser. The committee considered that THMD types 2, 3 and 5 are, in the worst case scenario, serious conditions**,** in the same manner as Thiamine-responsive Megaloblastic Anaemia, OMIM #249270, as they are severe and debilitating.

2.3. The committee considered that, due to THMD4 being a milder form of the condition, whereby individuals can lead a relatively normal life and recovery is possible, not to approve this for PGD.

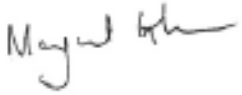
2.4. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a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

- Thiamine-responsive Megaloblastic Anaemia, OMIM #249270
- Thiamine Metabolism Dysfunction Syndrome 2 OMIM #607196
- Thiamine Metabolism Dysfunction Syndrome 3, OMIM #607196
- Thiamine Metabolism Dysfunction Syndrome 5, OMIM #614458

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

22 October 2018