Statutory Approvals Committee - minutes

Guys Hospital (0102)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) – application to perform PGT-M for 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency: MCC1D, OMIM #210200

Date:	28 February 2023
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams
Committee Members:	Jonathan Herring (Chair) Gudrun Moore Frances Flinter Catharine Seddon Geeta Nargund
Specialist Adviser:	Alan Fryer
Legal Adviser:	Eve Piffaretti - Blake Morgan LLP
Members of the Executive:	Moya Berry - Committee Officer
Observers:	Julia Chain - Chair (HFEA)
Apologies:	No apologies were received for the meeting
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:

- HFEA Code of Practice 9th edition
- Standard Licensing and Approvals Pack

The following papers were considered by the committee:

- Executive Summary
- PGT-M Application Form
- Redacted Peer Review
- Genetic Alliance (UK) Statement (NB the GA statement was received after the papers had been prepared)
- Research Paper provided by the applicants: 3-methylcrotonyl-CoA carboxylase deficiency Clinical, biochemical, enzymatic, and molecular studies in 88 individuals, Grunert al, (2012), *Orphanet Journal of Rare Diseases 2012, **7**:31*

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 PGT-M application for 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200, 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 Genetic Alliance (UK) statement provided a perspective on the impact of the condition on patients, their families, and carers.

1.5. The committee had regard to its decision tree. The committee noted that the centre is licensed to carry out PGT-M. The committee was also satisfied that the centre has experience of carrying out PGT-M and that generic patient information about its PGT-M 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 Congenital Disorder of 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200, is inherited in an autosomal recessive manner, 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.

1.8. The committee noted that although the penetrance of the condition is low, expression is variable even within the same family.

1.9. Congenital Disorder of 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200 is characterised by episodes of metabolic disturbances that present with feeding difficulties, vomiting, excessive tiredness, and reduced muscle tone. In the worst-case scenario, if left untreated, those with a severe phenotype are at risk of a metabolic crisis that can result in seizures and coma and has proven to be fatal in infancy in some reported cases. There is also evidence that some children may present with developmental delay and behavioural problems, even if they have not had any recognised metabolic crises

1.10. There is no cure for the condition. If untreated, this disorder can lead to delayed development, seizures, and coma. Many of these complications can be prevented with early detection and lifelong management with a low protein diet and appropriate supplements.

1.11. The committee noted the executive's request to consider 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200, for inclusion on the list of conditions approved for PGT-M. The committee agreed to consider the application on this basis.

1.12. The committee noted the request of the peer reviewer to consider an additional condition on the list for which PGT- M can be applied. The condition 3-Methylcrotonyl-CoA Carboxylase 2 Deficiency; MCC2D, OMIM #210210 is inherited in an autosomal recessive manner, meaning there is a 25% chance of an embryo being affected by the condition in each pregnancy if each parent has a relevant mutation. The condition results in the same clinical manifestations and is clinically indistinguishable from 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency: MCC1D, OMIM #210200.

2. Decision

2.1. The committee considered that in the worst-case 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200 is a serious and potentially fatal neurological condition that can present from infancy or in childhood and requires prompt recognition in order to reduce/prevent developmental delay, seizures, and potentially fatal metabolic disturbance. Those with the condition will require life-long monitoring and potentially adherence to a restrictive diet, which may be extremely challenging. The committee considered the potential emotional, psychological, and physical impact on the quality of life of those affected with the condition and their families.

2.2. The committee considered the condition 3- Methylcrotonyl-CoA Carboxylase 2 Deficiency; MCC2D, OMIM #210210 which in the worst-case scenario is potentially life threatening and if untreated may lead to developmental delays, seizures, and coma.

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 abnormalities will, given the conditions' worst symptoms, have or develop a serious physical disability, a serious illness, or any other serious medical condition.

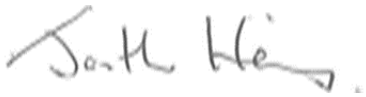
2.4. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act. The committee agreed to authorise testing for:

- 3-Methylcrotonyl-CoA Carboxylase 1 Deficiency; MCC1D, OMIM #210200
- 3-Methylcrotonyl-CoA Carboxylase 2 Deficiency; MCC2D, OMIM #210210

3. Chair's signature

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

Signature



Name

Jonathan Herring

Date

20 March 2023