Statutory Approvals Committee – minutes

Centre 0102 (Guys Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for

Muscular Dystrophy, Congenital, LMNA-related, (MDCL) OMIM #613205

Thursday, 25 January 2018

Church House Westminster, Dean's Yard, Westminster SW1P 3NZ

Committee members	Margaret Gilmore (Chair) Anne Lampe Tony Rutherford Ruth Wilde	
Members of the Executive	Dee Knoyle Bernice Ash Nana Gyamfi Chereena Harriott	Committee Secretary Committee Secretary (Observing) Licensing Information Officer (Observing) Inspections & Logistics Officer (Observing)
External adviser	Dr Alison Male	
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
- Genetic Alliance Statement

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Alison Male, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for Muscular Dystrophy, Congenital, LMNA-related, (MDCL), OMIM #613205 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 MDCL due to mutation of the LMNA gene is inherited in an autosomal dominant manner, which means there is 50% chance of having an affected child in each pregnancy, if either parent has a relevant mutation.

1.8. The committee noted that the application discusses that it is uncommon for those affected by the condition to have children. Cases generally arise either from de novo mutations – there is a 1-2% chance of an affected child being born to a couple who have already produced an affected child - or due to genetic mosaicism in one of the parents. In genetic mosaicism, a relevant mutation occurs in a cell in the early embryo, such that a subset of cells in the resulting adult contain the mutation. The adult may be unaffected if the mutated gene has no functional role in the affected cell subset, but can pass on the mutation if it is present in egg or sperm cells. An adult mosaic for MDCL will have up to a 50% chance of having an affected child in each pregnancy.

1.9. The committee noted that MDCL is a rare and severe genetic condition causing progressive muscle problems from birth or within the first few months of life. On the severe end of the scale, babies show reduced movements in the womb and are ‘floppy’ and weak at birth. Soon after, they develop contractures (loss of movement) in the joints and spine. Breathing muscles become weak, making them prone to chest infections and they generally need mechanical ventilation in early childhood. Affected individuals will require lifelong medical care.

1.10. The committee noted that symptoms of the condition MDCL include, hypotonia, congenital and progressive contractures, progressive limb weakness resulting in loss of ambulation, feeding difficulties requiring gastrostomy, respiratory failure requiring ventilation and cardiac arrhythmia with risk of sudden death. The condition is variable, but phenotype is fairly consistent. Penetrance is 100% for individuals with the particular LMNA mutation causing MDCL.

1.11. The committee noted that there is currently no treatment for the condition and only supportive care is available. Patients with this condition may never walk, or are likely to lose the ability to walk. All affected individuals are expected to need significant lifelong medical care. Serious cardiac arrhythmias are a possibility in older people, with the risk of sudden death. The impact of the condition on life expectancy has not been addressed in published studies, probably because the condition is rare, but is likely, given the symptoms, that life expectancy is significantly reduced.

1.12. The Peer Reviewer advised that mutations in the LMNA gene can cause several other conditions besides MDCL and some LMNA-associated phenotypes are relatively mild.

1.13. The Peer Reviewer also advised that there are many other types of congenital muscular dystrophy, some of which, like MDCL, are progressive and severe while others are relatively mild and non-progressive. All patterns of inheritance are represented in this diverse group of disorders.

1.14. The committee noted that the Executive provided a list of conditions which are already licensed for PGD by the HFEA, Table A:

TABLE A	
Condition	**OMIM number**
Emery-Dreifuss Muscular Dystrophy (x-linked) (EDMD) (Male embryos only)	#310100
Facioscapulohumeral Dystrophy (FSH)	#158900
Facioscapulohumeral Muscular Dystrophy Type 2	#158901
Merosin Deficient Congenital Muscular Dystrophy type 1A (MDC1A) (also known as LAMA2-related Muscular Dystrophy)	#607855
Muscular Dystrophy (Beckers)	#300376
Muscular Dystrophy (Duchenne)	#310200
Muscular Dystrophy (Oculopharangeal)	#164300
Muscular dystrophy, Limb-Girdle (LGMD) Type 1B	#159001
Muscular dystrophy-dystroglycanopathy, type A1 (Walker Warburg Syndrome)	#236670
Muscular dystrophy-dystroglycanopathy, type A3 (muscle-eye-brain disease)	#253280
Muscular dystrophy-dystroglycanopathy, type A5	#613153
Muscular dystrophy-dystroglycanopathy, types A2, A4, A6-A8 and A10-A14	#613150, #253800, #613154, #614643, #614830, #615041, #615181, #615249, #615287, #615350
Myotonic Dystrophy	#160900
Myotonic Dystrophy type 2	#602668
Rigid spine muscular dystrophy	#602771
Ullrich Congenital Muscular Dystrophy (UCMD)	#254090

1.15. The committee noted that the Executive also provided a list of similar conditions which are not on the HFEA approved PGD List of conditions, Table B:

TABLE B			
Condition	**OMIM number**	**Gene (OMIM number)**	**Inheritance**
Muscular Dystrophy, Congenital, LMNA-related, (MDCL) **– for cases where there is proven evidence of mosaicism in the blood or as a result of a second affected child**	#613205	LMNA (*150330)	Autosomal dominant
Emery-Dreifuss Muscular Dystrophy type 2 **– for cases where there is proven evidence of mosaicism in the blood or as a result of a second affected child**	#181350	LMNA (*150330)	Autosomal dominant
Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B1	#613155	POMT1 (*607423)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B2	#613156	POMT2 (*607439)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B3	#613151	POMGNT1 (*606822)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (congenital with or without mental retardation), type B5	#606612	FKRP (*606596)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B6	#608840	LARGE (*860590)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B14	#615351	GMPPB (*615320)	Autosomal recessive
Muscular dystrophy, congenital, due to Integrin alpha-7 deficiency	#613204	ITGA7 (*600536)	Autosomal recessive
Muscular dystrophy, congenital, megaconial type	#602541	CHKB (*612395)	Autosomal recessive
Muscular dystrophy, congenital, with cataracts and intellectual disability	#617404	INPP5K (*607875)	Autosomal recessive
Muscular dystrophy, congenital, Davignon-Chauveau type	#617066	TRIP4 (*604501)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (limb-girdle), type C1	#609308	POMT1 (*607423).	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (limb-girdle), type C5	#607155	FKRP (*606596)	Autosomal recessive
Muscular dystrophy-dystroglycanopathy (limb-girdle), type C7	#616052	ISPD (*614631)	Autosomal recessive
Muscular dystrophy, limb-girdle, type 2C	#253700	SGCG (*608896)	Autosomal recessive
Muscular dystrophy, limb-girdle, type 2S	#615356	TRAPPC11 (*614138)	Autosomal recessive
Emery-Dreifuss Muscular Dystrophy type 3	#616516	LMNA (*150330)	Autosomal recessive

1.16. The committee noted that the peer reviewer states that Emery-Dreifuss Muscular Dystrophy (X-linked) due to mutation in the Emerin gene is already licensed for PGD, however two autosomal forms of this condition due to mutation in LMNA, Emery-Dreifuss Muscular Dystrophy type 2 (OMIM #181350) and Emery-Dreifuss Muscular Dystrophy type 3 (OMIM #616516), are not licensed. The peer reviewer considers these two conditions to be similar to Emery-Dreifuss Muscular Dystrophy (X-linked) and the Executive has also listed them in Table B for the committee's consideration.

1.17. The committee noted the inspectorate's request to consider whether Muscular Dystrophy, Congenital, LMNA-related, (MDCL), OMIM #613205 and all of the conditions listed in Table B should be approved for inclusion on the PGD List. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that Muscular Dystrophy, Congenital, LMNA-related, (MDCL), OMIM #613205 is serious given that it is present at birth and causes progressive muscle problems, weakening the limbs and muscles used to breath and presenting feeding difficulties. The committee considered that affected individuals require lifelong medical care and usually do not reproduce due to their condition. There is also a risk of sudden death due to heart problems.

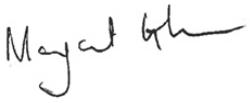
2.2. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented and advice provided by its Specialist Adviser, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, 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 condition Muscular Dystrophy, Congenital, LMNA-related, (MDCL), OMIM #613205 and the conditions listed in Table B above, which are similar, meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing for them.

2.3. The committee highlighted that the authorisation for testing Muscular Dystrophy, Congenital, LMNA-related, (MDCL), OMIM #613205 and Emery-Dreifuss Muscular Dystrophy type 2, OMIM #181350 is on the basis that there is proven evidence of mosaicism in the patient's blood or as a result of a second affected child.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

9 February 2018