# Statutory Approvals Committee - minutes

## Centre 0044 (The Centre for Reproductive and Genetic Health)

## Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) - application for Autosomal Recessive Congenital Titinopathies

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| Date: | 26 August 2021 |
| Venue: | HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams |
| Committee Members: | Margaret Gilmore (Chair)<br>Emma Cave<br>Anne Lampe<br>Ruth Wilde<br>Tim Child |
| Specialist Adviser: | Alan Fryer |
| Legal Adviser: | Tom Rider - FieldFisher LLP |
| Members of the Executive: | Moya Berry - Committee Officer<br>Catherine Burwood - Licensing Manager |
| 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
- Supporting paper provided by the applicant - Oates et al, 2018
- Supporting paper provided by the applicant - Fernandez–Marmiesse et al, 2017
- Supporting paper provided by the specialist adviser - Chauveau et al, 2014
- 2021-02-25 Statutory Approvals Committee Minutes, PGD for Myofibrillar Myopathy -9 with early respiratory failure (MFM9), OMIM #603689

## 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 Autosomal Recessive Congenital Titinopathy, 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 the condition is stated in the application and the peer review to be a newly characterised condition, not yet listed on the OMIM website, and not yet assigned a phenotypic OMIM number; however, several papers have been published on this condition in peer reviewed journals. The condition is caused by homozygous or compound heterozygous mutations in the Titin gene (TTN, OMIM gene number *188840).

**1.5.** The committee noted the application is being made at this time to allow PGT-M treatment to be provided to a family affected by the condition and the application states: ‘In the family for which the licence application is based, the genes mutations are likely to cause fetal demise’.

**1.6.** The committee noted that a Genetic Alliance (UK) statement had not been provided for this application.

**1.7.** 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.

**1.8.** 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 Autosomal Recessive Congenital Titinopathy 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.

**1.10.** The committee noted that the penetrance of the condition is 100%.

**1.11.** Autosomal Recessive Congenital Titinopathy is a potentially lethal condition. Common symptoms of the condition are excess fluid in a fetus, multiple joint contractures (present at birth or developing later) and cardiac abnormalities (both congenital malformations and the development of childhood-onset dilated cardiomyopathy). Low muscle tone and progressive muscle weakness affects the limbs as well as the axial musculature, which can result in scoliosis (curvature of the spine), and the respiratory muscles, which can result in respiratory insufficiency. The severity of the condition could result in fetal loss or neonatal death. Cardiomyopathy can lead to death in childhood or the requirement for cardiac transplantation.

**1.12.** There is no curative treatment and lifelong care will be needed. Severe fetal or neonatal abnormalities may result in fetal or neonatal death.

**1.13.** The committee noted the executive's request to consider Autosomal Recessive Congenital Titinopathy for inclusion on the list of conditions approved for PGT-M. With regard to the absence of an OMIM number for Autosomal Recessive Congenital Titinopathies, the specialist adviser brought to the committee's attention, a very similar condition called Salih myopathy OMIM #611705, described in a paper titled 'Recessive TTN truncating mutations define novel forms of core myopathy with heart disease' by Chauveau et al. The paper which was circulated to the committee prior to the meeting, details a number of individual cases, one of which is very similar in presentation to the description of Autosomal Recessive Congenital Titinopathy in the academic papers supplied by the applicant. The committee agreed to consider the application on this basis.

## 2. Decision

**2.1.** The committee considered that, in the worst-case scenario, Autosomal Recessive Congenital Titinopathy, is a rare condition with symptoms presenting in utero or at birth. There is no cure for the condition which can be fatal in children or in utero. Those who do survive may require ventilation as a result of respiratory failure and, in some cases, those affected may require heart transplant as a result of cardiac involvement or suffer an early cardiac death. The committee considered the potential significant, emotional, and physical implications, on the quality of life of those affected by the condition.

**2.2.** 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 condition's worst symptoms, have or develop a serious physical disability, a serious illness, or any other serious medical condition. The committee was therefore satisfied that the following condition does meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act.

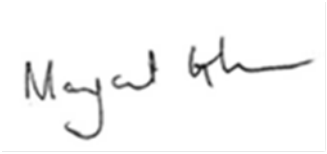
**2.3.** The committee was therefore satisfied that the following condition meets the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise it for testing.

**2.4.** The committee would like to ask the centre to confirm whether it agrees that Salih myopathy, OMIM #611705, could be used as a suitable name for the condition. If the centre agrees, the condition would be added to the PGT-M list as Salih myopathy, OMIM #611705. Alternatively, the committee agreed that the condition would be added to the PGT-M list as Autosomal Recessive Congenital Titinopathy and the committee in the latter scenario would request the executive approach OMIM for provision of a new number.

## 3. Chair's signature

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

**Signature**



**Name**

Margaret Gilmore

**Date**

21 September 2021