Statutory Approvals Committee - minutes

TFP Oxford Fertility (0035)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) – application to perform PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966

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
- 2022-02-24, Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked 1; XLID1, OMIM #309530
- 2020-07-30, Statutory Approvals Committee, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Claes-Jensen Type; MRXSCJ, OMIM #300534
- 2020-06-25, Statutory Approvals Committee Minutes, PGT-M for Aarskog-Scott Syndrome; AAS, OMIM #305400
- 2018-03-22 Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Snijders Blok Type; MRXSSB, OMIM #300958
- 2018-03-22, Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Nascimento Type; MRXSN, OMIM #300860
- 2017-04-27, Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic 34; MRXS34, OMIM #3009672016-06-24, SAC Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Lubs Type; MRXSL, OMIM #300260
- 2016-06-24 Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Lubs Type; MRXSL, OMIM #300260
- 2015-07-30, Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked, Syndromic, Christianson Type; MRXSCH, OMIM #300243
- 2014-03-27, Statutory Approvals Committee Minutes, PGT-M for Intellectual Developmental Disorder, X-Linked 109; XLID109, OMIM #309548

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 Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966, 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 Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966, is inherited in an X-linked recessive manner. This means there is a 50% chance of the abnormality being inherited in each pregnancy when the mother is a carrier. Males inheriting a TAF1 abnormality will be affected by MRXS33; females inheriting the abnormality will be carriers of the condition. It has been reported that a small number of female carriers manifest features of the condition to some degree,

1.8. The committee noted that the penetrance of the condition appears to be 100% in males.

1.9. Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966 is a neurodevelopmental disorder characterised by delayed psychomotor development, intellectual disability, and characteristic facial features, and follows X-linked recessive inheritance. The condition typically presents in infancy with hypotonia and delayed development and subsequently the affected male has severe intellectual disability with autistic behaviour and may have impaired movement. Feeding difficulties (dysphagia) may occur. Congenital heart disease appears to be a common feature and can lead to early fatality. Affected children require long term supervised care and special education and are unable to lead independent lives. Those with seizures require antiepileptic medication. For some, normal mobility is not possible.

1.10. The committee noted the executive's request to consider Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966, for inclusion on the list of conditions approved for PGT-M. The committee agreed to consider the application on this basis.

1.11. The committee also noted the request of the peer reviewer to consider an additional thirty-one conditions for inclusion on the list for which PGT-M can be applied. The conditions are:

- Intellectual Developmental Disorder, X-Linked, Syndromic, Pilorge Type; MRXSP, OMIM #301076
- Intellectual Developmental Disorder, X-Linked, Syndromic, Houge Type; MRXSHG, OMIM #301008
- Intellectual Developmental Disorder, X-Linked, Syndromic, Snyder-Robinson Type; MRXSSR, OMIM #309583
- MEHMO Syndrome; MEHMO, OMIM #300148
- Van Esch-O'Driscoll Syndrome; VEODS, OMIM #301030
- Partington Syndrome; PRTS, OMIM #309510
- Intellectual Developmental Disorder, X-Linked, Syndromic, Hedera Type; MRXSH, OMIM #300423
- Renpenning Syndrome 1; RENS1, OMIM #309500
- Intellectual Developmental Disorder, X-Linked, Syndromic, Turner Type; MRXST, OMIM #309590
- Intellectual Developmental Disorder, X-Linked, Syndromic, Siderius Type; MRXSSD, OMIM #300263
- Intellectual Developmental Disorder, X-Linked Syndromic 16; MRXS16, OMIM #305400
- Wieacker-Wolff Syndrome; WRWF, OMIM #314580
- Intellectual Developmental Disorder, X-Linked, Syndromic, Wilson-Turner Type; WTS, OMIM #309585
- Intellectual Developmental Disorder, X-Linked, Syndromic, Billuart Type; MRXSBL, OMIM #300486
- Intellectual Developmental Disorder, X-Linked, Syndromic, Lujan-Fryns Type; MRXSLF, OMIM #309520
- Tonne-Kalscheuer Syndrome; TOKAS, OMIM #300978
- Arts Syndrome; ARTS, OMIM #301835
- Intellectual Developmental Disorder, X-Linked, Syndromic 14; MRXS14, OMIM #300676
- Intellectual Developmental Disorder, X-Linked, Syndromic, Hackmann-Di Donato Type; MRXSHD, OMIM #301039

- Intellectual Developmental Disorder, X-Linked, Syndromic, Cabezas Type; MRXSC, OMIM #300354
- Intellectual Developmental Disorder, X-Linked, Syndromic, Wu Type; MRXSW, OMIM #300699
- Intellectual Developmental Disorder, X-Linked, Syndromic, Raymond Type; MRXSR, OMIM #300799
- Borjeson-Forssman-Lehmann Syndrome; BFLS, OMIM #301900
- Intellectual Developmental Disorder, X-Linked, Syndromic 13; MRXS13, OMIM #300055
- Intellectual Developmental Disorder, X-Linked, Syndromic, 35; MRXS35, OMIM #300998
- Intellectual Developmental Disorder, X-Linked, Syndromic, Armfield Type; MRXSA, OMIM #300261
- Lissencephaly, X-Linked, 2; LISX2, and Hydranencephaly with Abnormal Genitalia, OMIM #300215
- Intellectual Developmental Disorder, X-Linked 29; XLID29, OMIM #300419
- Corpus Callosum, Agenesis of, with Abnormal Genitalia, OMIM #300004
- Opitz-Kaveggia Syndrome; OKS, OMIM #305450
- Ohdo Syndrome, X-Linked; OHDOX, OMIM #300895

1.12. The above condition types are all inherited in an X-linked recessive manner. This means there is a 50% chance of the abnormality being inherited in each pregnancy when the mother is a carrier. Males inheriting such an abnormality will be affected and females inheriting the abnormality will be carriers of the condition. For most of the conditions female carriers are usually asymptomatic.

1.13. The conditions are all characterised by intellectual disability presenting in childhood and in most of the conditions, both in general and in the worst-case scenario, the severity of the intellectual disability is at least as severe as the primary condition applied for, Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966. The peer reviewer has stated that many of these conditions are syndromic, i.e. they are associated with other clinical features, which vary between the condition types. However, most frequently, the clinical features include developmental delay, speech difficulties, various congenital malformations and seizures. Males affected by the following conditions can have reduced life expectancy.

1.14. The committee discussed further two of the conditions listed above; Intellectual Developmental Disorder, X-Linked, Syndromic, Siderius Type; MRXSSD, OMIM #300263 and Intellectual Developmental Disorder, X-Linked Syndromic 16; MRXS16, OMIM #305400 as these conditions are considered to be slightly milder in their phenotype compared to Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966. However, based on the advice of the specialist adviser, the committee agreed these conditions are associated with significant levels of learning disability, which may affect the quality of life of those affected.

1.15. The committee acknowledged the extensive and comprehensive work carried out by the Peer Reviewer and the Specialist Adviser in the analysis of these conditions and wished to convey its appreciation and thanks.

2. Decision

2.1. The committee considered that, in the worst-case scenario Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966, is a potentially life limiting disorder that can present from birth or in infancy. Those affected suffer global developmental delay and severe intellectual disability requiring life-long support and care. Significant mobility issues may also arise. Those affected may also experience seizures and severe behavioural difficulties. 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 following conditions:

- Intellectual Developmental Disorder, X-Linked, Syndromic, Pilorge Type; MRXSP, OMIM #301076
- Intellectual Developmental Disorder, X-Linked, Syndromic, Houge Type; MRXSHG, OMIM #301008
- Intellectual Developmental Disorder, X-Linked, Syndromic, Snyder-Robinson Type; MRXSSR, OMIM #309583
- MEHMO Syndrome; MEHMO, OMIM #300148
- Van Esch-O'Driscoll Syndrome; VEODS, OMIM #301030
- Partington Syndrome; PRTS, OMIM #309510
- Intellectual Developmental Disorder, X-Linked, Syndromic, Hedera Type; MRXSH, OMIM #300423
- Renpenning Syndrome 1; RENS1, OMIM #309500
- Intellectual Developmental Disorder, X-Linked, Syndromic, Turner Type; MRXST, OMIM #309590
- Intellectual Developmental Disorder, X-Linked, Syndromic, Siderius Type; MRXSSD, OMIM #300263
- Intellectual Developmental Disorder, X-Linked Syndromic 16; MRXS16, OMIM #305400
- Wieacker-Wolff Syndrome; WRWF, OMIM #314580
- Intellectual Developmental Disorder, X-Linked, Syndromic, Wilson-Turner Type; WTS, OMIM #309585
- Intellectual Developmental Disorder, X-Linked, Syndromic, Billuart Type; MRXSBL, OMIM #300486
- Intellectual Developmental Disorder, X-Linked, Syndromic, Lujan-Fryns Type; MRXSLF, OMIM #309520
- Tonne-Kalscheuer Syndrome; TOKAS, OMIM #300978
- Arts Syndrome; ARTS, OMIM #301835
- Intellectual Developmental Disorder, X-Linked, Syndromic 14; MRXS14, OMIM #300676
- Intellectual Developmental Disorder, X-Linked, Syndromic, Hackmann-Di Donato Type; MRXSHD, OMIM #301039
- Intellectual Developmental Disorder, X-Linked, Syndromic, Cabezas Type; MRXSC, OMIM #300354
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- Intellectual Developmental Disorder, X-Linked, Syndromic, Raymond Type; MRXSR, OMIM #300799
- Borjeson-Forssman-Lehmann Syndrome; BFLS, OMIM #301900
- Intellectual Developmental Disorder, X-Linked, Syndromic 13; MRXS13, OMIM #300055
- Intellectual Developmental Disorder, X-Linked, Syndromic, 35; MRXS35, OMIM #300998

- Intellectual Developmental Disorder, X-Linked, Syndromic, Armfield Type; MRXSA, OMIM #300261
- Lissencephaly, X-Linked, 2; LISX2, and Hydranencephaly with Abnormal Genitalia, OMIM #300215
- Intellectual Developmental Disorder, X-Linked 29; XLID29, OMIM #300419
- Corpus Callosum, Agenesis of, with Abnormal Genitalia, OMIM #300004
- Opitz-Kaveggia Syndrome; OKS, OMIM #305450
- Ohdo Syndrome, X-Linked; OHDOX, OMIM #300895

which in the worst-case scenario are potentially life limiting conditions that present in childhood and lead to serious global developmental delay and intellectual disability.

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:

- Intellectual Developmental Disorder, X-Linked, Syndromic 33; MRXS33, OMIM #300966
- Intellectual Developmental Disorder, X-Linked, Syndromic, Pilorge Type; MRXSP, OMIM #301076
- Intellectual Developmental Disorder, X-Linked, Syndromic, Houge Type; MRXSHG, OMIM #301008
- Intellectual Developmental Disorder, X-Linked, Syndromic, Snyder-Robinson Type; MRXSSR, OMIM #309583
- MEHMO Syndrome; MEHMO, OMIM #300148
- Van Esch-O'Driscoll Syndrome; VEODS, OMIM #301030
- Partington Syndrome; PRTS, OMIM #309510
- Intellectual Developmental Disorder, X-Linked, Syndromic, Hedera Type; MRXSH, OMIM #300423
- Renpenning Syndrome 1; RENS1, OMIM #309500
- Intellectual Developmental Disorder, X-Linked, Syndromic, Turner Type; MRXST, OMIM #309590
- Intellectual Developmental Disorder, X-Linked, Syndromic, Siderius Type; MRXSSD, OMIM #300263
- Intellectual Developmental Disorder, X-Linked Syndromic 16; MRXS16, OMIM #305400
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- Ohdo Syndrome, X-Linked; OHDOX, OMIM #300895

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