Statutory Approvals Committee - minutes

Centre 0005 (Fertility Exeter)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) – application to perform PGT-M for 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300

Date:	27 May 2025
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams
Committee Members:	Frances Flinter (Chair) Tim Child Graham James Geeta Nargund Anya Sizer
Specialist Adviser:	Ed Blair
Legal Adviser:	Tine Whitman - Blake Morgan LLP
Members of the Licensing Team:	Moya Berry - Committee Officer Caroline Pringle - Licensing Manager
Observers:	Miranda MacFarlane - Policy Officer
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
- Further comments received from the centre via email
- Redacted Peer Review
- Genetic Alliance (UK) Statement **(NB the GA statement was received after the papers had been prepared and forwarded to the committee members)**
- 2010-06-24 Licence Committee Minutes, PGT-M application for 'Pseudovaginal Perineoscrotal Hypospadias due to 5-Alpha-Reductase Deficiency (insofar as that condition affects males, with simultaneous sex determination)', OMIM #264600

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Dr Ed Blair, 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 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300, 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 noted that there will be two proposed purposes of testing as defined by the Act. Firstly, to test the embryos 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' and secondly under the purpose of testing the embryos as set out in paragraph 1ZA(1)(c) of Schedule 2 of the Act i.e. 'to establish the sex of the embryo in cases where there is a particular risk that any resulting child will have or develop:

i. A gender related serious physical or mental disability
ii. A gender related serious illness
iii. Any other gender-related serious medical condition.

1.6. 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.

1.7. The committee noted that, 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300, is inherited in an autosomal recessive manner and where both parents are carriers of the condition there is a 1 in 4 (25%) chance their embryo will inherit both copies of the genetic abnormality. However, the condition only affects male embryos and there would be a 1 in 2 (50%) chance that the embryo has XY chromosomes. There is therefore a 1 in 8 (12.5%) chance the patient couple will have an affected child in each pregnancy, if each parent has a relevant mutation.

1.8. The committee noted that the peer reviewer has stated that the penetrance for genetic males is very high (i.e. almost certainly close to 100%), though the degree to which virilisation (the development of male secondary sexual characteristics in a female) at puberty affects appearances is likely variable. For genetic females the penetrance can be considered very different and is probably much lower. The data on this is sparse but intuitively it is certainly possible that there are mild, undiagnosed cases in the general population. However, technically a 'mild' case is not one that is non-penetrant, so it is difficult putting a figure on penetrance for genetic females.

1.9. 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300, is one of the many varieties of 'Disorders of Sex Development' (DSDs) and is sometimes referred to as a form of 'male pseudohermaphroditism. It follows autosomal recessive inheritance and the problem arises because of defective or inadequate synthesis of the 'male' hormone, testosterone, in the testes. The result is that individuals who are 'chromosomal males' (46, XY) are under-masculinised. They may be born looking like phenotypic females, i.e. female external genitalia (the prostate does not develop, and neither is there a uterus), and if a gender-determining genetic test had been performed in pregnancy the appearance would be totally unexpected and result in investigations. Alternatively, the newborn baby may present with under-masculinised male genitalia and hypospadias (ambiguous genitalia), which would also result in appropriate investigations. Otherwise, a chromosomal male with this condition who has normal looking female genitalia will likely be raised as a female. There is a possibility that an examination during childhood detects suspected testes in the inguinal canals (groins) or labial folds, which again could lead to investigations. If not, when the individual reaches puberty and the expected onset of menstruation does not occur, investigations are then initiated. The other consequence of the hormonal changes at puberty is that significant quantities of another male hormone, androstenedione, occurs in the testes, which results in virilisation of the body generally – including the genitalia – and hirsutism (male pattern secondary sexual hair). When this occurs and a diagnosis is made the major difficulty faced is whether the individual continues as a 'female' or changes to 'male' identity. Virilisation of the genitalia is not usually complete, so 'corrective surgery' might be undertaken to conform to a female appearance or perhaps enhanced to be more male in appearance. There is/are, apparently, case(s) where the individual has at puberty assumed a male identity successfully. Where surgery has been performed the individual was infertile, which is clearly a significant consequence of the condition in genetic males. Another potential consequence is the risk of a testicular cancer in cases where the testes remain undescended long term. It is also possible for chromosomal females (46,XX) to have this metabolic disorder. These individuals undergo normal pubertal breast development but, like genetic males, undergo virilisation at puberty with hirsutism as well as menstrual disorders due to the sudden increase of ovarian androstenedione production, which may convert to testosterone. This can result in polycystic ovarian syndrome (PCOS) with secondary amenorrhoea (an abnormal absence of menstruation), which could result in subfertility but perhaps not necessarily complete infertility.

1.10. There is no cure for 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300. Management includes psychological support for the child and parents and multidisciplinary care by a Disorders of Sex Development (DSD) team including paediatric endocrinologists, paediatric urologists/gynaecologists, clinical psychologists and clinical geneticists. Those with severe hypospadias are offered a multistage surgical procedure or sometimes surgery is offered to make the external genitalia appear more typically female or male. The testes may be removed to reduce the risk of cancer and virilisation at puberty. Hormonal treatment may be needed to block testosterone in girls who do not have a gonadectomy (the surgical removal of

one or both reproductive organs) and to give them oestrogen to promote breast development. Those raised as boys usually need testosterone supplementation at puberty, given by injection.

1.11. The committee noted the inspectorate's request to consider 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300, for inclusion on the list of conditions approved for PGT-M and to consider testing under paragraph 1ZA(1)(c) of Schedule 2 of the Act. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that in the worst-case scenario 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300 is a serious condition that can be detected from birth and have a significant, and lasting effect on individuals and their lives. Those with the condition are born genetically male but have ambiguous or female genitalia and are highly likely to require a significant number of complex and painful surgical procedures to correct the abnormalities and require lifelong hormonal treatment with regular monitoring. Those affected are also at an increased risk of testicular cancer where the testes remain undescended long term. Children who are considered to be girls from birth, can at puberty, experience virilisation, leading to symptoms such as increased muscle mass, deepening of the voice, and development of male-pattern facial and body hair. Individuals may face physical, medical, and psychological challenges through childhood, adolescence, and adulthood, including the knowledge of impaired fertility. The committee considered the potentially devastating emotional, psychological, and physical impact on the quality of life of those affected with the condition and their families.

2.2. In coming to its decision on whether the condition should be licensed the committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied (in relation to the condition being considered) that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk that a person with such abnormality will, given the condition's worst symptoms, have or develop a serious physical disability, a serious illness, or any other serious medical condition.

2.3. The committee then discussed whether to authorise 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300 to detect embryos that have XY chromosomes and have inherited biallelic variants in the HSD17B3 simultaneously. The committee considered the information provided in the application and received advice from its specialist adviser, and noted the information provided by the applicants.

2.4. The committee considered whether the condition 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300 met the statutory requirements that it is required to assess when considering applications to undertake testing to establish the sex of an embryo. These are whether there is a particular risk that any resulting child will have or develop:

i. A gender related serious physical or mental disability

ii. A gender related serious illness

iii. Any other gender-related serious medical condition.

2.5. The committee noted that the condition can present a serious risk to male individuals and was satisfied that it had sufficient information at this time to authorise the condition for testing under the purpose described in paragraph 1ZA(1)(c) of Schedule 2 of the Act (i.e. medical sex selection) to detect embryos that have XY chromosomes and have inherited biallelic variants in the HSD17B3 simultaneously.

2.6. The committee was therefore satisfied that the following condition meets the criteria under paragraph 1ZA(1)(b) of Schedule 2 of the Act. **AND** under paragraph 1ZA(1)(c) of Schedule 2 of the Act for sex selection. The committee agreed to authorise testing for:

- 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300
- 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, OMIM #264300 to detect embryos that have XY chromosomes and have inherited biallelic variants in the HSD17B3 simultaneously.

3. Chair's signature

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

Signature

Name Frances Flinter

Date

17 June 2025