Statutory Approvals Committee - minutes

The Centre for Reproductive and Genetic Health Trading as CRGH Portland (0044)

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) – application to perform PGT-M for 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 and Adrenal Insufficiency, NR5A1-Related, OMIM #612964

Date:	29 October 2024
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Microsoft Teams
Committee Members:	Geeta Nargund (Chair) Alex Kafetz Tim Child Graham James
Specialist Adviser:	Alan Fryer
Legal Adviser:	Martin Sleight - FieldFisher LLP
Members of the Licensing Team:	Moya Berry - Committee Officer Catherine Burwood - Licensing Manager
Observer:	Tom Fowler - HFEA Authority Member (Induction)
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
- Research paper provided by the applicants: Role of NR5A1 Gene Mutations in Disorders of Sex
- Development: Molecular and Clinical Features Luppino et al, *Curr. Issues Mol. Biol.* (2024) 46, 4519–4532
- 16 public comments received via email.
- 2019-08-29 Statutory Approvals Committee Minutes, PGT-M application for Adrenal Insufficiency, Congenital, with 46, XY Sex Reversal, Partial or Complete, OMIM #613743
- 2016-01-28 Statutory Approvals Committee Minutes, PGT-M application for 46, XY Sex Reversal 6 (SRXY6), OMIM #613762
- 2005-12-19 Licence Committee Minutes, PGT-M application for Adrenal Hyperplasia, Congenital, due to 21-Hydroxylase Deficiency, OMIM #201910

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 NR5A1 Related Sex Reversal (XX or XY) and Adrenal Insufficiency, OMIM *184757, is consistent with the peer review.

1.3. The committee noted that the conditions being applied for are 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. The committee also noted the comments provided by members of the public, which provided a further perspective on the impact of the condition on patients and their families.

1.5. The committee noted that gene, OMIM *184757 is associated with the five following phenotypes on OMIM: 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, 46, XY Sex Reversal 3 (SRXY3), OMIM #612965, Adrenal Insufficiency, NR5A1-Related, OMIM #612964, Premature Ovarian Failure 7 (POF7), OMIM #612964 and Spermatogenic Failure 8 (SPGF8), OMIM #613957. However, the peer reviewer has stated that this application appears to be specifically requesting to licence only the first three conditions i.e. Premature Ovarian Failure 7 (POF7), OMIM #612964 and Spermatogenic Failure 8 (SPGF8), OMIM #613957. Therefore, the committee agreed to only consider.

- 46, XX Sex Reversal 4 (SRXX4), OMIM #617480
- 46, XY Sex Reversal 3 (SRXY3), OMIM #612965
- Adrenal Insufficiency, NR5A1-Related, OMIM #612964

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 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'.

1.8. The committee noted that, the conditions 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 and Adrenal Insufficiency, NR5A1-Related, OMIM #612964, are all inherited in an autosomal dominant manner, which means there is a 50% chance of an embryo being affected by the conditions in each pregnancy if either parent has a relevant mutation.

1.9. The committee noted that the expressivity of the conditions linked to the NR5A1 gene is very variable, but the penetrance is high (though probably not 100%).

1.10. The most frequent clinical manifestations of 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 are ambiguous genitalia, followed by female external genitalia with clitoromegaly (enlarged clitoris); the third most common presentation is apparent sex reversal compared with karyotype (apparently normal female external genitalia) and the fourth is a child with male genitalia and hypospadias (where the opening of the urethra is on the underside of the penis instead of at the tip) and the hypospadias may sometimes be associated with micropenis and absent testes. 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, is associated with virilisation of female genitalia. Whilst the child is chromosomally female, she may have testes and absent internal female genitalia. Patients with either SRXY3 or SRXX4 may inherit the mutant NR5A1 gene from an asymptomatic or mildly symptomatic, fertile mother or father. Apart from the effect on the development of the external and internal genitalia, mutations in the NR5A1 gene may result in delayed sexual development, delayed or abnormal puberty, growth delay and infertility.

1.11. Adrenal insufficiency has been recorded in patients with a clinical picture of disordered genital development but also in those with normal development of the genitalia. Symptoms of adrenal insufficiency may include hypotonia (decreased muscle tone) and typical laboratory findings of decreased sodium, increased potassium, and elevated adrenocorticotropic hormone (ACTH) in blood samples. Hyperpigmentation, salt-wasting crisis, prolonged jaundice (a yellow discoloration of the body tissue resulting from the accumulation of excess bilirubin), hypoglycemia (where the blood glucose level is lower than the standard range) and vomiting have also been noted. Adrenal failure is a rare but potentially life-threatening condition in patients with NR5A1 mutations.

1.12. There are no cures for 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 and Adrenal Insufficiency, NR5A1-Related, OMIM #612964, and treatment is symptom-specific. Difficult decisions and choices may need to be made with regard to gender of rearing and some patients have their gender reassigned later in life. Surgical procedures, replacement therapy for adrenal insufficiency if present, and sex hormone therapy according to the specifics of the case, may be treatment options. These treatments help to normalise appearances and avoid adrenal insufficiency crises but will not correct structural defects in reproductive organs and infertility. Fertility preservation is a consideration in some patients. Psychological issues related to the condition may be lifelong.

1.13. The committee noted the inspectorate's request to consider 46, XX Sex Reversal 4 (SRXX4), OMIM #617480, 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 and Adrenal Insufficiency, NR5A1-Related, OMIM #612964, for inclusion on the list of conditions approved for PGT-M. The committee agreed to consider the applications on this basis.

2. Decision

2.1. The committee considered that, in the worst-case scenario 46, XX Sex Reversal 4 (SRXX4), OMIM #617480 and 46, XY Sex Reversal 3 (SRXY3), OMIM #612965 can present at birth. Those with either condition can be born with ambiguous genitalia requiring a significant number of complex and painful surgical procedures to correct the abnormalities, which may not always be successful. Those with the condition are also at risk of suffering a life-threatening adrenal crisis. Lifelong hormonal treatment for adrenal insufficiency may be required as well as sex hormones, which will require regular monitoring. Individuals may face these physical, medical, and psychological challenges through childhood, adolescence, and adulthood, including the knowledge of impaired fertility in some cases. The committee considered the potential emotional, psychological, and physical impact on the quality of life of those affected with the conditions and their families.

2.2. The committee considered that in the worst-case scenario Adrenal Insufficiency, NR5A1-Related, OMIM #612964, is a potentially debilitating condition that can present in the neonatal period or develop during later childhood or adulthood. Those affected are at risk of suffering a life-threatening adrenal crisis requiring prompt treatment. Lifelong hormonal treatment for adrenal insufficiency may be required. The committee considered the potential emotional, psychological, and physical impact on the quality of life of those affected with the condition and their families.

2.3. 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 conditions being considered) 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 under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act. The committee agreed to authorise testing for:

- 46, XX Sex Reversal 4 (SRXX4), OMIM #617480,
- 46, XY Sex Reversal 3 (SRXY3), OMIM #612965,
- Adrenal Insufficiency, NR5A1-Related, OMIM #612964

3. Chair's signature

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

Signature

Name

Geeta Nargund

Date

20 November 2024