Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307

Thursday, 28 June 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Anthony Rutherford Ruth Wilde	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood Richard Chamberlain	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer) Temporary Committee Clerk (Induction)
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Tom Rider	Fieldfisher 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
- Additional paper from peer reviewer (Table 1)
- Comment from centre regarding peer review
- One patient comment
- Genetic Alliance UK Statement
- SAC minutes 28 September 2017: Congenital Deafness with inner ear agenesis, microtia and microdontia, OMIM #610706.
- SAC minutes 28 September 2017: Non Syndromic Congenital Deafness (DFNB29), OMIM #614035.
- SAC minutes 27 July 2017 and 29 June 2017: Non-syndromic Sensorineural Hearing Loss (DFNA6), OMIM # 600965
- Licence Committee minutes 10 October 2001: Autosomal Recessive Non-syndromic sensorineural deafness (now defined in the PGD list as Autosomal recessive Deafness Type 1A (DFNB1A), OMIM #220290.

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 application for PGD for TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307 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 the condition is inherited in an autosomal recessive pattern which means there is a 25% chance of an embryo being affected with the condition in each pregnancy, if both parents have a relevant mutation.

1.8. The committee noted that TPRN-associated autosomal recessive non-syndromic deafness (DFNB79) is a hereditary form of hearing loss. It causes bilateral severe to profound sensorineural hearing loss affecting all hearing frequencies. Onset of hearing loss is pre-lingual, usually from birth. The condition is progressive, with the level of hearing loss most often being profound, either from birth, or progressing to profound deafness during childhood and into the teenage years

1.9. Those with less severe degrees of hearing loss at diagnosis usually will progress from severe to profound deafness.

1.10. The committee noted that no curative treatment is available and the condition is managed as with any other child with severe deafness, with early intervention being key. This may include hearing aids and vibrotactile devices. Because of the level of severity of hearing loss with this condition, most individuals will be offered cochlear implantation at some point. Cochlear implantation is a safe and effective operation in the majority of cases, although it can be associated with device breakdown, skin flap breakdown and local site reactions all of which may need a further operation. Infection in the form of otitis media and mastoiditis can be very painful and require prolonged treatment and about 0.1% of cases will be affected by meningitis which can in some cases be fatal. Sufferers will require special help with education and, while the goal of treatment is mainstream schooling, many are likely to attend schools for children with severe hearing loss. Affected children have hearing loss before they learn to speak, which can cause social isolation and delay in speech and language development. Most individuals will need to adapt many of their life choices to meet the challenges of their hearing loss.

1.11. The committee noted that the Peer Reviewer had listed a further 35 loci associated with prelingual severe to profound non-syndromic deafness inherited in an autosomal recessive manner. One of these, OMIM #612645, is already licensed for PGD. The Peer Reviewer noted that ‘The rest along with TPRN-associated AR non-syndromic deafness are clinically indistinguishable.’, recommending that they are all considered and licensed, stating that they ‘respectfully suggest that the committee makes a decision to either licence them all or to remove OMIM #612645 from the list of approved

conditions.' These subtypes, with the exception of OMIM #612645, are not currently approved for PGD and are listed in Table 1 below:

TABLE 1

LOCUS	**OMIM #**
DFNB105	616958
DFNB12	601386
DFNB48	609439
DFNB 29	614035
DFNB53	609706
DFNB66	610212
DFNB59	610220
DFNB88	615429
DFNB102	615974
DFNB15	601869
DFNB1	220290
DFNB1	**612645**
DFNB32/82	608565
DFNB39	608265
DFNB67	610265
DFNB63	611451
DFNB97	616705
DFNB74	613718
DFNB3	600316
DFNB30	607101
DFNB22	607039
DFNB9	601071
DFNB23	609533
DFNB70	614934
DFNB24	611022
DFNB104	616515
DFNB68	610419
DFNB61	613865
DFNB16	603720
DFNB21	603629
DFNB86	614617
DFNB7/11	600974

DFNB99	616178
DFNB 6	600971
DFNB28	609823
DFNB18	602092

1.12. The committee noted that OMIM #612645 relates in the OMIM system to Deafness, Autosomal Recessive 1B (DFNB1B), which does not appear on the list of conditions approved for PGD, and the executive was unable to locate evidence that it has ever been approved. OMIM #220290, relates to Deafness, Autosomal Recessive 1A; (DFNB1A) which is on the HFEA list of conditions approved for PGD. The committee noted that confusion between the two conditions may have occurred, but the executive considered that this does not undermine the Peer Reviewer's point that the conditions on the list are clinically indistinguishable from each other, and from the condition which is the primary subject of the application: DFNB79, OMIM #613307.

1.13. The committee noted that the PGD lead at the centre confirmed, on behalf of the Person Responsible (PR), that they would like the 34 loci associated with prelingual severe to profound non-syndromic autosomal recessive deafness, listed in Table 1 and which are not yet approved for PGD, to also be considered as conditions for which PGD can be applied; along with the initial application for TPRN-associated autosomal recessive non-syndromic deafness (DFNB79).

1.14. The committee also noted the approval of two other comparable conditions, non-syndromic Sensorineural Hearing Loss, #OMIM #600965, for a specific family with a severe presentation and Congenital Deafness with inner ear agenesis, microtia and microdontia, OMIM #610706. It was also noted that non-syndromic Congenital Deafness (DFNB29), #OMIM #614035) was recently not approved for addition to the PGD list.

1.15. The committee welcomed the advice of the Specialist Advisor, who clarified that the conditions listed at Table 1 were not likely to all be of a progressive nature, but would generate the same issues, for the individual and the family, as TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307. However, for clarification on the symptoms of each stated condition, a more detailed analysis would be required. The Specialist Advisor indicated that currently there were around 90 conditions listed on OMIM as forms of autosomal recessive deafness and so he was not sure whether the list given at Table 1 may be incomplete or whether the ones listed were only those that always or typically resulted in pre-lingual hearing loss.

1.16. The committee noted the inspectorate's request to consider whether TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307 should be approved for inclusion on the PGD List. The inspectorate also requested that the committee considers approving the other 34 loci associated with non-syndromic autosomal recessive deafness (listed in Table 1 and where they are not already approved for PGD) can also be approved for PGD.

1.17. The committee noted that Deafness, Autosomal Recessive 99; DFNB99, does not appear to have a phenotypic OMIM # number allocated within the OMIM website. The Peer Reviewer has identified it using an OMIM gene number *616178.

1.18. The committee noted the executive's suggestion that, should the applications not be approved, they might wish to consider removing Deafness, Autosomal Recessive 1A; (DFNB1A) (OMIM #220290) from the list of conditions approved for PGD.

2. Decision

2.1. The committee conducted an exceptionally long deliberation, and by a majority vote, they considered that, in the worst case scenario, TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307 is serious given Cochlear implants cannot be inserted until a child reaches the age of one, resulting in the infant losing a crucial first year of hearing as onset of the condition can be prelingual. Implants are not a cure, do not eradicate hearing distortions and further operations can become necessary. The condition can cause profound deafness from birth, is progressive and fatal meningitis can be a very rare complication of a likely intervention. The condition may be socially isolating and may severely impact the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to approve the 34 conditions associated with non-syndromic autosomal recessive deafness listed in Table 1. The committee agreed not to licence these additional conditions, adjourning the decision. The committee noted the peer reviewer's comment that the conditions are "clinically indistinguishable", but felt they lacked clear, detailed information and evidence to support this view. The committee requested a second peer review to be conducted, on these suggested additional conditions, by a different peer reviewer, and for these to be presented to them for further consideration for licensing for PGD.

2.3. The committee agreed that Deafness, Autosomal Recessive 1A; (DFNB1A) (OMIM #220290) should remain on the list of conditions approved for PGD.

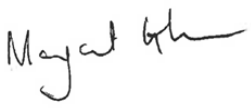
2.4. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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 TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307 meets the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act.

2.5. The committee agreed to authorise testing for TPRN-associated autosomal recessive non-syndromic deafness (DFNB79), OMIM #613307.

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

30 July 2018