Statutory Approvals Committee – minutes

Centre 0201 (Edinburgh Assisted Conception Unit)

Pre-implantation Genetic Diagnosis (PGD) application for

Congenital hereditary cataract, type 10 (CTRCT10), OMIM #600881

Thursday, 30 August 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Ruth Wilde Anthony Rutherford	
Members of the Executive	Bernice Ash Paula Robinson Catherine Burwood	Committee Secretary Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Jane Williams	Mills & Reeve LLP
Observers	Stevan Cirkovic	Policy Officer (Induction)

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
- Genetic Alliance UK statement
- SAC minutes, 28 January 2016: PGD for congenital cataracts caused by mutations within the GJA3 gene, OMIM #601885

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 Congenital hereditary cataract, types 6, 9, 10-12, 14-19, 21-23, 30, 33, 34, 38-42, 44 and 45, as listed in the table below, is consistent with the peer review:

Condition	OMIM number
Congenital hereditary cataract, type 6 (CTRCT6)	#116600
Congenital hereditary cataract, type 9 (CTRCT9)	#604219
Congenital hereditary cataract, type 10 (CTRCT10))	#600881
Congenital hereditary cataract, type 11 (CTRCT11)	#610623
Congenital hereditary cataract, type 12 (CTRCT12)	#611597
Congenital hereditary cataract, type 14 (CTRCT14)	#601885
Congenital hereditary cataract, type 15 (CTRCT15)	#615274
Congenital hereditary cataract, type 16 (CTRCT16)	#613763
Congenital hereditary cataract, type 17 (CTRCT17)	#611544
Congenital hereditary cataract, type 18 (CTRCT18)	#610019
Congenital hereditary cataract, type 19 (CTRCT19)	#615277
Congenital hereditary cataract, type 21 (CTRCT21)	#610202
Congenital hereditary cataract, type 22 (CTRCT22)	#609741
Congenital hereditary cataract, type 23 (CTRCT23)	#610425
Congenital hereditary cataract, type 30 (CTRCT30)	#116300
Congenital hereditary cataract, type 33 (CTRCT33)	#611391
Congenital hereditary cataract, type 34 (CTRCT34)	#612968
Congenital hereditary cataract, type 38 (CTRCT38)	#614691
Congenital hereditary cataract, type 39 (CTRCT39)	#615188
Congenital hereditary cataract, type 40 (CTRCT40)	#302200
Congenital hereditary cataract, type 41 (CTRCT41)	#116400
Congenital hereditary cataract, type 42 (CTRCT42)	#115900
Congenital hereditary cataract, type 44 (CTRCT44)	#616509
Congenital hereditary cataract, type 45 (CTRCT45)	#616851

1.3. The committee noted that the centre applied primarily for CTRCT type 10, OMIM #600881 to be considered for approval as a patient is awaiting treatment for this condition. The centre then added CTRCT types 9, 11, 12, 14-19, 21-23, 30, 33, 34, 38-42, 44 and 45 as additional types of the condition, though no patients are awaiting treatment for these.

1.4. The committee noted that CTRCT types 6, 9, 10-12, 15-19, 21-23, 30, 33, 34, 38-42, 44 and 45 are not on the list of conditions approved for PGD. Congenital cataracts, OMIM #601885 (i.e. CTRCT type 14), has already been approved for PGD and minutes of this decision were before the committee and noted.

1.5. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application.

1.6. 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.

1.7. 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 CTRCT types 6, 10-12, 15, 21, 23, 30, 39, 41 and 42, are inherited in an autosomal dominant pattern which means there is a 50% chance of an embryo being affected with the condition in each pregnancy, if either parent has a relevant mutation.

1.9. The committee noted that CTRCT types 18, 19, 34, 38, 44 and 45 are 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.

1.10. The committee noted that CTRCT types 9, 16, 17, 22 and 33 can show either autosomal dominant or autosomal recessive modes of inheritance, depending on the causative gene mutation(s).

1.11. The committee noted that CTRCT type 40 is inherited in an X-linked pattern which means there is a 25% chance of an embryo being affected in each pregnancy, if the mother is a carrier of a relevant mutation. Affected children will be males.

1.12. The committee noted that, at worst, congenital hereditary cataracts cause opacity of the eye lens presenting at birth or early in infancy. The cataracts/opacities impair vision directly and interfere with the early development of vision. They can eventually lead to blindness, particularly if there are secondary complications such as glaucoma or if associated with other congenital abnormalities of the eye such as microphthalmia. They may require surgical removal soon after birth, after which children require artificial lens implantation or the use of glasses or contact lenses. Diagnosis and surgery can be a distressing and traumatic experience for children and their parents. Surgery may lead to complications. Even when surgery is uncomplicated, the outcome is not always good, and visual Impairment may still occur.

1.13. Symptoms in all types of congenital hereditary cataracts include cloudy and blurred vision with some patients being registered blind. Congenital cataracts can have a severe impact on children and families.

1.14. CTRCT10, the primary condition applied for, is caused by CRYBA1 pathogenic mutations inherited in an autosomal dominant manner. Data on penetrance are limited but the CTRCT10 is fully penetrant in three generations in the family requesting PGD for CTRCT10.

1.15. The committee noted that regarding congenital hereditary cataracts types generally, penetrance figures are unknown but variable expressivity has been described for several types. CTRCT types which are inherited in an autosomal recessive manner are likely to be highly penetrant.

1.16. The committee noted the table below, prepared by the executive, presenting information from the OMIM website and in the centre's application showing the genetic aetiology in each CTRCT type:

Condition	OMIM number	Gene/ Locus (OMIM gene number)	[1]Inheritance pattern
CTRCT6	#116600	EPHA2; *176946	AD
CTRCT9	#604219	CRYAA; *123580	AD; AR
CTRCT10	#600881	CRYBA1; *123610	AD
CTRCT11	#610623	PITX3; *602669	AD
CTRCT12	#611597	BFSP2; *603212	AD
CTRCT14	#601885	GJA3; *121015	AD
CTRCT15	#615274	MIP; *154050	AD
CTRCT16	#613763	CRYAB; *123590	AD; AR
CTRCT17	#611544	CRYBB1; *600929	AD; AR
CTRCT18	#610019	FYCO1; *607182	AR
CTRCT19	#615277	LIM2; *154045	AR
CTRCT21	#610202	MAF *177075	AD
CTRCT22	#609741	CRYBB3; *123630	AD; AR
CTRCT23	#610425	CRYBA4; *123631	AD
CTRCT30	#116300	VIM; *193060	AD
CTRCT33	#611391	BFSP1; *603307	AD; AR
CTRCT34	#612968	FOXE3; *601094	AR
CTRCT38	#614691	AGK; *610345	AR
CTRCT39	#615188	CRYGB; *123670	AD
CTRCT40	#302200	NHS; *300457	X-linked
CTRCT41	#116400	WFS1; *606201	AD
CTRCT42	#115900	CRYBA2; *600836	AD
CTRCT44	#616509	LSS; *600909	AR
CTRCT45	#616851	SIPA1L3; *616655	AR

AD – autosomal dominant AR – autosomal recessive

1.17. The committee also noted that the Peer Reviewer commented that CTRCT types 6, 9, 10-12, 15-19, 21-23, 30, 33, 34, 38-42, 44 and 4, would be appropriate conditions for PGD.

1.18. The committee noted that CTRCT14, OMIM #601885, has already been approved for PGD because of 'the effect the condition has on a patient's vision and the need for multiple surgical intervention which has further associated risk'.

1.19. The executive had noted that, according to the OMIM website, CTRCT types 41, 42 and 45, have each been characterised only in one family.

1.20. The committee noted the inspectorate's request to consider whether the centre's primary application to add Congenital hereditary cataract, type 10 (CTRCT10), OMIM #600881 should be approved for inclusion on the PGD List. The inspectorate also requested the committee consider approving the additional forms of Congenital hereditary cataract. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Congenital hereditary cataract, type 10 (CTRCT10), OMIM 600881 is serious due to the condition's early onset, severely affecting the child, even when treatment is conducted promptly. The condition may require numerous surgical interventions and treatments, which can result in several complications and blindness. Cataract surgery may not fully restore vision. In the worst case scenario, the condition has a severe impact on the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to approve the additional CTRCT types 9, 11-12, 14-19, 21-23, 30, 33, 34, 38-42, 44 and 45. The committee considered that CTRCT types 9, 11-12, 14-19, 21-23, 30, 33, 34 38-40 and 44 are, in the worst case scenario, serious conditions as they have a severe impact on the individual and can lead to blindness.

2.3. The committee decided that, as CTRCT types 41, 42 and 45 had each been characterised in only one family according to OMIM and no patients with these types were awaiting treatment at the applicant centre, these conditions would not be approved for licensing for PGD at this time.

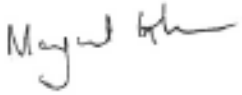
2.4. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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 following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing:

- Congenital hereditary cataract, type 6 (CTRCT6), OMIM #116600
- Congenital hereditary cataract, type 9 (CTRCT9), OMIM #604219
- Congenital hereditary cataract, type 10 (CTRCT10), OMIM #600881
- Congenital hereditary cataract, type 11 (CTRCT11), OMIM #610623
- Congenital hereditary cataract, type 12 (CTRCT12), OMIM #611597
- Congenital hereditary cataract, type 15 (CTRCT15), OMIM #615274
- Congenital hereditary cataract, type 16 (CTRCT16), OMIM #613763
- Congenital hereditary cataract, type 17 (CTRCT17), OMIM #611544
- Congenital hereditary cataract, type 18 (CTRCT18), OMIM #610019
- Congenital hereditary cataract, type 19 (CTRCT19), OMIM #615277
- Congenital hereditary cataract, type 21 (CTRCT21), OMIM #610202
- Congenital hereditary cataract, type 22 (CTRCT22), OMIM #609741
- Congenital hereditary cataract, type 23 (CTRCT23), OMIM #610425
- Congenital hereditary cataract, type 30 (CTRCT30), OMIM #116300
- Congenital hereditary cataract, type 33 (CTRCT33), OMIM #611391
- Congenital hereditary cataract, type 34 (CTRCT34), OMIM #612968
- Congenital hereditary cataract, type 38 (CTRCT38), OMIM #614691
- Congenital hereditary cataract, type 39 (CTRCT39), OMIM #615188
- Congenital hereditary cataract, type 40 (CTRCT40), OMIM #302200
- Congenital hereditary cataract, type 44 (CTRCT44), OMIM #616509

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

26 September 2018