Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for

Leigh Syndrome, OMIM #256000 and

Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome), OMIM #616277

Thursday, 24 May 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood Mhairi West	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer) Inspector (Observer - Induction)
Specialist Adviser	Dr Ed Blair	
Legal Adviser	Sarah Ellson	Fieldfisher LLP
Observers	Shamima Rahman	Specialist Adviser

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
- Clarification from centre re OMIM numbers
- Email from centre with statement to be added to the application re the application scope
- Redacted Peer Review
- Extra statement from Peer Reviewer
- Comment from centre re peer review and statement
- Genetic Alliance UK Statement
- 31 August 2017, SAC Minutes, Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome) OMIM #252010
- 23 January 2017, SAC Minutes, Leigh Syndrome, French Canadian type (LSFC) OMIM #220111
- 26 August 2010, LC Minutes, Leigh Syndrome (Infantile Subacute Necrotising Encephalopathy) OMIM *185620

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 application for PGD for Leigh syndrome, OMIM #256000 and Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome), OMIM #616277 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 may be inherited in an autosomal recessive pattern which means there is a 25% chance of an embryo being affected with the condition if each parent has a relevant mutation. X-linked types carry an up to 50% chance of having an affected child in each pregnancy if the mother is a carrier as symptoms of varying severity may also be seen in females inheriting the mutation.

1.8. The committee noted that Leigh syndrome is an early-onset, severe, progressive neurodegenerative condition. Symptoms manifest from infancy and become progressively more severe. Leigh syndrome, OMIM #256000, can be caused by mutations in multiple nuclear and mitochondrial DNA encoded genes, which affect the pathway by which mitochondria produce metabolic energy. The various different mitochondrial complex deficiency pathways all lead to the phenotype of Leigh syndrome.

1.9. The committee noted that Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome) is a type of Leigh syndrome. Symptoms include feeding problems, vomiting, failure to gain weight, hypotonia (decreased muscle tone), seizures (which are difficult to control), developmental delay, visual impairment and hearing loss. Later there is regression, with loss of skills, spasticity (muscles continuously contract), ataxia (lack of voluntary control of muscle movements), optic atrophy, cranial nerve palsies, cardiac involvement, and eventually encephalopathy (brain damage) with loss of consciousness. Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome) is 100% penetrant. The order in which symptoms can appear may vary, and in the early days it may be difficult to make a diagnosis because the symptoms are non-specific. Prognosis is poor, resulting in severe disability and early death.

1.10. The committee noted that there is no curative treatment, only supportive and early death (in infancy or childhood) is usual.

1.11. The committee noted that the Peer Reviewer focused on Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome) but also commented on Leigh syndrome, covering multiple causes and the possibility of licensing Leigh syndrome, OMIM #256000, to cover multiple causative mutations.

1.12. The committee noted that the Peer Reviewer considered that other forms of Leigh Syndrome could also be suitable for licensing, and are currently not approved for PGD. These conditions are as follows:

Condition	OMIM	Gene affected
Mitochondrial Complex II Deficiency	#252011	SDHA, SDHD, SDHAF1
Mitochondrial Complex III Deficiency	#124000	BCS1L
Mitochondrial Complex IV Deficiency	#220110	COA7, COX20, FASTKD2, COX8A, COX14, APOPT1, SCO1, COX10, TACO1, PET100, COX6B1
Mitochondrial Complex V Deficiency	#604273	ATPAF2
Combined Oxidative Phosphorylation Deficiency 15 (COXPD15)	#614947 (*611766)	MTFMT
Coenzyme Q10 Deficiency, Primary, 1	#607426	COQ2
Dihydrolipoamide Dehydrogenase Deficiency (DLDD)	#246900	DLD
Pyruvate Dehydrogenase, Alpha-1 (PDHA1)	#312170	PDHA1

1.13. The committee noted that a consultant in Clinical Genetics and Genomics at the centre confirmed, on behalf of the Person Responsible (PR), that they would like the additional conditions to also be considered as conditions for which PGD can be applied.

1.14. The committee noted that Autosomal Recessive Mitochondrial Complex 1 Deficiency (Complex 1 Deficient Leigh Syndrome) OMIM #252010; Leigh syndrome (Infantile Subacute Necrotising Encephalopathy) OMIM *185620; Leigh syndrome, French Canadian type (LSFC) OMIM #220111 and Leigh's (subacute necrotising encephalopathy of childhood) OMIM #516000, #516002, #516005 and #516006 are already approved for PGD.

1.15. The committee noted the inspectorate's request to consider whether Leigh syndrome OMIM #256000 and Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome), OMIM #616277 should be approved for inclusion on the PGD List. The inspectorate also requested that the committee considers approving the additional forms of Leigh syndrome listed in the table above, which have the same severe clinical outcome. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Leigh syndrome OMIM #256000 and Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome), OMIM #616277 are serious given they have an early onset, with a multifaceted impact, causing symptoms including feeding problems, visual impairment, seizures and brain damage. The committee noted death in early childhood is the norm. The conditions severely impact on the individual's quality of life and the family.

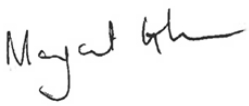
2.2. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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:

- Leigh syndrome OMIM #256000
- Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D; Leigh syndrome), OMIM #616277
- Mitochondrial Complex II Deficiency, OMIM #252011
- Mitochondrial Complex III Deficiency, OMIM #124000
- Mitochondrial Complex IV Deficiency, OMIM #220110
- Mitochondrial Complex V Deficiency, OMIM #604273
- Combined Oxidative Phosphorylation Deficiency 15 (COXPD15), OMIM #614947
- Coenzyme Q10 Deficiency, Primary, 1, OMIM #607426
- Dihydrolipoamide Dehydrogenase Deficiency (DLDD), OMIM #246900
- Pyruvate Dehydrogenase, Alpha-1 (PDHA1), OMIM #312170

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

19 June 2018