Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for Amyotrophic Lateral Sclerosis (ALS) 6, OMIM #608030

Thursday, 27 September 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Ruth Wilde	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Specialist Adviser	Professor Peter Turnpenny	
Legal Adviser	Dawn Brathwaite	Mills & Reeve 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
- Millecamps 2010 – additional paper provided by the peer reviewer
- Genetic Alliance UK statement
- Email from centre confirming including additional subtypes of ALS to be included in the application.
- SAC minutes 31 March 2016, PGD for Amyotrophic Lateral Sclerosis Frontotemporal Dementia 1, OMIM #105550
- LC minutes 30 June 2011, PGD for ALS1

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Professor Peter Turnpenny 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 Amyotrophic Lateral Sclerosis (ALS) 6, OMIM #608030 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 conditions being applied for are 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 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.

1.8. The committee noted that ALS6 is caused by mutations in the Fused in Sarcoma (*FUS*) gene which is dominantly inherited and almost all gene mutation carriers will develop ALS; i.e. there is a 50% chance of having an affected child in each pregnancy, if either parent has a relevant mutation, and the mutation is highly penetrant. It is a progressive neurodegenerative disease which affects the motor neurons in the brain and spinal cord. The motor neurons are nerve cells which communicate instructions from the brain that control muscle movement. Affected individuals usually present with muscular weakness causing foot-drop or poor handgrip, and slurred speech. Wasting and weakness spreads to affect all other muscle groups leading to complete paralysis. Death due to respiratory muscle weakness occurs 3-5 years after symptom onset. The average age of onset is around 50 years in those with a family history, however sometimes the symptoms can develop from teenage years to middle age.

1.9. Symptoms of the condition include: limb muscle wasting; weakness and cramps; exaggerated deep tendon reflexes and spasticity; wasting and weakness of the tongue causing slurred speech; choking and difficulty swallowing. There are a number of different types of ALS in addition to type 6, characterised by the different causative gene mutations and inheritance patterns. Penetrance isn't available for all the rarer subtypes but appears to be high.

1.10. The committee noted there is no treatment and only palliative measures are available, focussed on symptom control. Patients need a multidisciplinary approach involving neurology, speech therapy, physiotherapy, nutritional advice and psychological support. Drugs may include antidepressants, baclofen and benzodiazepines to relieve spasticity and muscle cramps. Swallowing difficulties can be alleviated with thickened liquids, pureeing food and finally a gastrostomy tube. Computer assisted devices may help communication and other mechanical devices such as wheelchairs, lifts and bathrooms aids may help daily living. Patients may need ventilation support and hospice care. This is a severe neurological condition which causes severe disability, impacting significantly on the quality of life, and early death.

1.11. The committee noted that ALS1 and Frontotemporal dementia and/or amyotrophic lateral sclerosis 1 have already been approved for PGD, acknowledging the minutes included in the papers.

1.12. The committee noted that the Peer Reviewer was provided with information from the OMIM website on the other ALS types, not currently licensed (including ALS6), and which may be suitable for licensing because they have genetically characterised causative genes, rather than susceptibility factors. The Peer Reviewer was asked whether these ALS types were suitable for approval for PGD. The information, provided to the Peer Reviewer, is provided in Tables A and b below. The clinical features and age of onset, stated in Table A, were provided by the Peer Reviewer:

Table A: ALS types with clinical features and age of onset, which are potentially suitable for licensing for PGD. Data from the OMIM website and relevant publications

ALS type	OMIM #	Inheritance pattern	Clinical Features	Age at onset (years)
Frontotemporal dementia and/or ALS 2	615911	AD	Frontotemporal dementia, cerebellar ataxia, myopathy, and motor neuron disease consistent with amyotrophic lateral sclerosis.	50s
ALS 2, juvenile	205100	AR	Progressive spasticity, wheelchair use in childhood / teens, distal muscular atrophy, bulbar involvement, dysarthria, in some leading to inability to speak. Normal cognition.	early childhood
Frontotemporal dementia and/or ALS 3	616437	AD	Cognitive impairment, behavioral abnormalities, Frontotemporal dementia, and speech apraxia and/or upper and lower motor neuron signs. Some patients Paget disease of bone.	50-70
Frontotemporal dementia and/or ALS 4	616439	AD	50% Frontotemporal dementia, bulbar symptoms 87%, dysarthria, upper and lower motor neuron symptoms	mean 60
ALS 4, juvenile	602433	AD	Chronic motor neuron disease characterized by combined upper and lower motor neuron symptoms and signs. Difficulty walking, muscle wasting, loss of hand function. Slowly progressive. Wheelchair 6th decade. Most normal lifespan. Bulbar sparing.	2nd decade
ALS 5, juvenile	602099	AR	Slowly progressive. Wheelchair some 5th decade. Some lose hand function. Normal cognition.	2nd decade
ALS 6, with or without frontotemporal	608030		Average survival 33 months. Rapidly progressive. distal weakness, proximal fasciculations, and decreased reflexes, respiratory	average 40s, some teens

dementia			failure. Frontotemporal dementia in some.	
ALS 8	608627	AD	Lower motor neuron, speech and swallowing affected, slowly progressive, respiratory failure.	31-45
ALS 9	611895		Classic signs of ALS, including progressive upper and lower motor neuron loss affecting the limbs, but 1 patient presented with parkinsonism and later developed signs of frontotemporal dementia.	
ALS 10, with or without frontotemporal dementia	612069	AD	Rapidly progressive, bulbar symptoms prominent, Frontotemporal dementia common. 4-7 years to death.	mean 47
ALS 11	612577	AD	Predominantly neurological, bulbar	40-77
ALS 12	613435		Relatively slow progression, muscle weakness, dysphagia, intubation, reported case bed bound from 30s frontotemporal dementia.	30-60
ALS 14, with or without frontotemporal dementia	613954		Lower motor neuron dysfunction resulting in rapidly progressive paralysis and death from respiratory failure, bulbar features, early-onset Paget disease and frontotemporal dementia.	37-53
ALS 15, with or without frontotemporal dementia	300857	XLD	Males and females affected, females later, Frontotemporal dementia, behavioural symptoms, motor disability /spastic paralysis, bulbar. Death within 17 years.	
ALS 16, juvenile	614373	AR	Lower limb spasticity with hyperreflexia and weakness were noted at the age of 1 to 2 years. By age 9 or 10, affected individuals showed weakness of the hand and forearm muscles, which progressed to paralysis of the forearm extensors and triceps. By the age of 20 years, 2 patients used wheelchairs. None of the patients had respiratory or bulbar muscle weakness. cognition was preserved.	early childhood
ALS 17	614696	AD	Frontotemporal dementia, progressive neurodegenerative disorder with predominantly lower motor neuron involvement, manifest as muscle weakness and wasting of the upper and lower limbs, bulbar signs, and respiratory insufficiency.	adult
ALS 18	614808		Limb onset > bulbar	30-40
Amyotrophic	615515	AD	Relatively slowly progressive upper	60-70

lateral sclerosis 19			and lower motor neuron involvement without cognitive impairment. Two patients became ventilator-dependent and all 3 developed the locked-in state.	
ALS 20	615426	AD	Muscle, bone, brain and motor neurons that was clinically indistinguishable from previous families we have seen with *VCP*-related MSP.	
ALS 21	606070	AD	Upper and lower motor neurons, resulting in muscle weakness and respiratory failure. Some patients may develop myopathic features or dementia. vocal cord and pharyngeal weakness.	mean 42
ALS 22 with or without frontotemporal dementia	616208	AD	All patients carrying TUBA4A mutations had spinal-onset classical ALS with upper and lower motor neuron signs. Two cases also developed a cognitive decline of frontal type, consistent with a diagnosis of frontotemporal dementia.	
ALS 23	617839	AD	Classic ALS disease symptoms without dementia, and both bulbar and limb onset occurred.	average 67

Table B: The ALS types, as also listed in Table A, with known genetic causes, which are potentially suitable for licensing for PGD. Data from the OMIM website.

Phenotype	**OMIM #**	**Gene/Locus**	**Gene OMIM**
Frontotemporal dementia and/or ALS 2	615911	*CHCHD10, FTDALS2, SMAJ, IMMD*	615903
ALS 2, juvenile	205100	*ALS2, ALSJ, PLSJ, IAHSP*	606352
Frontotemporal dementia and/or ALS 3	616437	*SQSTM1, P62, PDB3, FTDALS3, NADGP, DMRV*	601530
Frontotemporal dementia and/or ALS 4	616439	*TBK1, NAK, FTDALS4, IIAE8*	604834
ALS 4, juvenile	602433	*SETX, SCAR1, AOA2, ALS4*	608465
ALS 5, juvenile	602099	*SPG11, KIAA1840, FLJ21439, ALS5, CMT2X*	610844
ALS 6, with or without frontotemporal dementia	608030	*FUS, TLS, ALS6, ETM4*	137070
ALS 8	608627	*VAPB, VAPC, ALS8*	605704
ALS 9	611895	*ANG, RNASE5, ALS9*	105850
ALS 10, with or without	612069	*TARDBP, TDP43, ALS10*	605078

frontotemporal dementia			
ALS 11	612577	*FIG4, KIAA0274, SAC3, ALS11, YVS, BTOP*	609390
ALS 12	613435	*OPTN, GLC1E, FIP2, HYPL, NRP, ALS12*	602432
ALS 14, with or without frontotemporal dementia	613954	*VCP, IBMPFD1, ALS14, CMT2Y*	601023
ALS 15, with or without frontotemporal dementia	300857	*UBQLN2, PLIC2, CHAP1, ALS15*	300264
ALS 16, juvenile	614373	*SIGMAR1, SRBP, ALS16, DSMA2*	601978
ALS 17	614696	*CHMP2B, DMT1, VPS2B, ALS17*	609512
ALS 18	614808	*PFN1, ALS18*	176610
ALS 19	615515	*ERBB4, HER4, ALS19*	600543
ALS 20	615426	*HNRNPA1, IBMPFD3, ALS20*	164017
ALS 21	606070	*MATR3, MPD2, ALS21*	164015
ALS 22 with or without frontotemporal dementia	616208	*TUBA4A, TUBA1, ALS22*	191110
ALS 23	617839	*ANXA11, ANX11, ALS23*	602572

1.13. The Peer Reviewer agreed that all the ALS types in Tables A and B should be considered for licensing as conditions for which PGD can be applied, commenting that, “Mutations in the genes in the top section (i.e. listed in both Tables A and B) are all reported to cause ALS. The age of onset is variable with some causing juvenile ALS and others with a later onset. The rate of progression also differs. Most are associated with FTD (fronto-temporal dementia) and some with Paget’s disease of the bone (weak bone leading to pain and deformity). There is a huge overlap in clinical features and often they are clinically indistinguishable and only genetic testing enables subtyping.”

1.14. The committee welcomed the advice of the Specialist Adviser who raised some concern regarding ALS 12 as this condition had an unknown pattern of inheritance. The committee was also informed that both ALS 16 and ALS 20 had only been characterised in one family in each case. The Specialist Adviser confirmed that all the remaining ALS types listed would be suitable for PGD, and had been identified in more than one population.

1.15. The committee noted that the Person Responsible (PR) had confirmed, by email, that the following conditions should be included in the application:

- Frontotemporal dementia and/or amyotrophic lateral sclerosis 2, OMIM #615911
- Amyotrophic lateral sclerosis 2, juvenile, OMIM # 205100
- Frontotemporal dementia and/or Amyotrophic lateral sclerosis 3, OMIM # 616437
- Frontotemporal dementia and/or Amyotrophic lateral sclerosis 4, OMIM # 616439
- Amyotrophic lateral sclerosis 4, juvenile, OMIM # 602433
- Amyotrophic lateral sclerosis 5, juvenile, OMIM # 602099
- Amyotrophic lateral sclerosis 8, OMIM # 608627
- Amyotrophic lateral sclerosis 9, OMIM # 611895
- Amyotrophic lateral sclerosis 10, with or without frontotemporal dementia OMIM, # 612069
- Amyotrophic lateral sclerosis 11, OMIM # 612577
- Amyotrophic lateral sclerosis 12, OMIM # 613435
- Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia, OMIM # 613954
- Amyotrophic lateral sclerosis 15, with or without frontotemporal dementia, OMIM # 300857

- Amyotrophic lateral sclerosis 16, juvenile, OMIM # 614373
- Amyotrophic lateral sclerosis 17, OMIM # 614696
- Amyotrophic lateral sclerosis 18, OMIM # 614808
- Amyotrophic lateral sclerosis 19, OMIM # 615515
- Amyotrophic lateral sclerosis 20, OMIM # 615426
- Amyotrophic lateral sclerosis 21, OMIM # 606070
- Amyotrophic lateral sclerosis 22 with or without frontotemporal dementia, OMIM # 616208
- Amyotrophic lateral sclerosis 23, OMIM # 617839

1.16. The committee noted the inspectorate's request to consider whether the centre's primary application to add Amyotrophic Lateral Sclerosis (ALS) 6, OMIM #608030 should be approved for inclusion on the PGD List. The inspectorate also requested the committee consider approving the subsidiary application, for the ALS conditions stated in Tables A and B. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Amyotrophic Lateral Sclerosis (ALS) 6, OMIM #608030 is serious as it can have an early onset, affecting individuals in their 20's, is a chronic neurodegenerative disease, causing disintegration of the body, despite cognitive awareness fully remaining. Death can occur three to five years after initial symptoms present and there is no prospect of treatment. The condition severely impacts on the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to consider whether the additional conditions, stated in Tables A and B, should be added to the list of conditions for which PGD can be applied. The committee agreed that, in the worst can scenario, the conditions are serious due to their progressive and chronic nature.

2.3. The committee considered that, due to ALS type 12 having an unknown pattern of inheritance, and types 12 and 16 each only being characterised in one family, not to approve these conditions for licensing for PGD at this time.

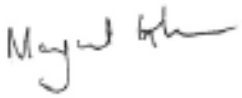
2.4. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a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

- Amyotrophic Lateral Sclerosis (ALS) 6, OMIM #608030
- Frontotemporal dementia and/or amyotrophic lateral sclerosis 2, OMIM #615911
- Amyotrophic lateral sclerosis 2, juvenile, OMIM # 205100
- Frontotemporal dementia and/or Amyotrophic lateral sclerosis 3, OMIM # 616437
- Frontotemporal dementia and/or Amyotrophic lateral sclerosis 4, OMIM # 616439
- Amyotrophic lateral sclerosis 4, juvenile, OMIM # 602433
- Amyotrophic lateral sclerosis 5, juvenile, OMIM # 602099
- Amyotrophic lateral sclerosis 8, OMIM # 608627
- Amyotrophic lateral sclerosis 9, OMIM # 611895
- Amyotrophic lateral sclerosis 10, with or without frontotemporal dementia OMIM, # 612069
- Amyotrophic lateral sclerosis 11, OMIM # 612577
- Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia, OMIM # 613954
- Amyotrophic lateral sclerosis 15, with or without frontotemporal dementia, OMIM # 300857
- Amyotrophic lateral sclerosis 17, OMIM # 614696
- Amyotrophic lateral sclerosis 18, OMIM # 614808
- Amyotrophic lateral sclerosis 19, OMIM # 615515
- Amyotrophic lateral sclerosis 21, OMIM # 606070
- Amyotrophic lateral sclerosis 22 with or without frontotemporal dementia, OMIM # 616208
- Amyotrophic lateral sclerosis 23, OMIM # 617839

3. Chairs signature

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

Signature



Name

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Date

22 October 2018