Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier/Additional Provider

TEST – DISEASE/CONDITION – POPULATION TRIAD			
Submitting laboratory:	**Exeter RGC**	**Approved:**	**September 2012**
1. Disease/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	AARSKOG-SCOTT SYNDROME; AAS		
2. OMIM number for disease/condition	305400		
3. Disease/condition – please provide a brief description of the characteristics of the disease/condition and prognosis for affected individuals. Please provide this information in laymen's terms.	Aarskog-Scott syndrome mainly affects males and is characterised by distinctive facial features (dropping eyelids, widely spaced eyes, down-slanting eye slits, short nose), skeletal abnormalities (short fingers and toes, bent fingers), urogenital abnormalities (abnormal scrotum, undescended testes) and short stature. The symptoms of the condition can vary widely even within the same family. Females that carry the condition can have subtle facial features, short stature and widow's peak.		
4. Disease/condition – mode of inheritance	X-linked recessive		
5. Gene – approved name(s) and symbol as published on HUGO database (alternative names will be listed on the UKGTN website)	fyve, rhogef, and ph domain-containing 1; FGD1		
6. OMIM number for gene(s)	300546		
7. Gene – description(s)	Located on Xp11.22; size: 50.7Kb; 18 coding exons.		
7b. Number of amplicons to provide this test	19 amplicons		
7c. MolU/Cyto band that this test is assigned to	MOLU Band D 2012/13 GenU Band E 2013/14		
8. Mutational spectrum for which you test including details of known common mutations	Missense, nonsense, splicing and small insertion/deletion mutations. Partial and whole gene deletions.		
9. Technical method(s)	Sequencing of the entire coding region and conserved splice sites. Dosage analysis using MLPA.		
10. Validation process Please explain how this test has been validated for use in your laboratory	Sequence analysis for the identification of heterozygous and homozygous mutations is employed for screening of >40 genes in the laboratory.		
11a. Are you providing this test already?	Yes		
11b. If yes, how many reports have you produced?	5 (3 probands, 2 family members)		
11c. Number of reports mutation positive	4 (3 probands, 1 family member)		

11d. Number of reports mutation negative	1 (family member)
12. For how long have you been providing this service?	Since September 2011.
13a. Is there specialised local clinical/research expertise for this disease?	No.
13b. If yes, please provide details	
14. Are you testing for other genes/diseases/conditions closely allied to this one? Please give details	No.
Your current activity If applicable - How many tests do you currently provide annually in your laboratory?	Not known. (Testing started September 2011 – 5 samples in 4 months).
15a. Index cases	
15b. Family members where mutation is known	
Your capacity if Gene Dossier approved How many tests will you be able to provide annually in your laboratory if this gene dossier is approved and recommended for NHS funding?	
16a. Index cases	Unlimited
16b. Family members where mutation is known	Unlimited
Based on experience how many tests will be required nationally (UK wide) per annum? Please identify the information on which this is based	2-3 new cases a year (Orrico *et al* 2011 Eur J Hum Genet 19(11).
17a. Index cases	10
17b. Family members where mutation is known	10
18. National activity (England, Scotland, Wales & Northern Ireland) **If your laboratory is unable to provide the full national need please could you provide information on how the national requirement may be met.** For example, are you aware of any other labs (UKGTN members or otherwise) offering this test to NHS patients on a local area basis only? This question has been included in order to gauge if there could be any issues in equity of access for NHS patients. It is appreciated that some laboratories may not be able to answer this question. If this is the case please write "unknown".	Unknown. We would be able to meet the full national need. No other UK laboratories are currently providing this test.

EPIDEMIOLOGY

19. Estimated prevalence of condition in the general UK population Please identify the information on which this is based	1/25 000 (Orrico *et al* 2011 Eur J Hum Genet 19 (11).
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	29 molecularly proven cases have been published worldwide (Orrico *et al* 2010 Am J Med Genet 152A, 313-318).
21. Estimated penetrance Please identify the information on which this is based	Complete penetrance in all affected males reported so far.
22. Estimated prevalence of condition in the target population. The target population is the group of people that meet the minimum criteria as listed in the Testing Criteria.	Around 20% of individuals with a clinical diagnosis of AAS will have a *FGD1* mutation (Orrico *et al* 2011 Eur J Hum Genet 19 (11).

INTENDED USE

23. Please tick the relevant clinical purpose of testing		
Diagnosis	☒ **Yes**	☐ **No**
Treatment	☐ **Yes**	☒ **No**
Prognosis & management	☒ **Yes**	☐ **No**
Presymptomatic testing	☐ **Yes**	☒ **No**
Carrier testing for family members	☒ **Yes**	☐ **No**
Prenatal testing	☒ **Yes**	☐ **No**

TEST CHARACTERISTICS

24. Analytical sensitivity and specificity

This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

Single direction sequence analysis using Mutation Surveyor software - sensitivity 99% and specificity 99% (in-house data).

25. Clinical sensitivity and specificity of test in target population

The *clinical sensitivity* of a test is the probability of a positive test result when condition is known to be present; the *clinical specificity* is the probability of a negative test result when disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without condition (for specificity).

Orrico *et al* analysed the *FGD1* gene (by DHPLC and Sanger sequencing) in 60 apparently unrelated male patients with AAS. Mutations were identified in 11 probands (18.33%) and for probands where samples from family members were available the mother was always shown to be a carrier (Orrico *et al* 2010 Am J Med Genet 152A, 313-318). Combining this study with the groups other previously published data, in total 110 families have been tested 24 were found to have a pathogenic mutation (mutation detection rate of 21.8%) (Orrico *et al* 2011 Eur J Hum Genet 19 (11). Partial and whole gene deletions have been reported in FGD1 (Schwartz *et al* 2000 Eur J Hum Genet 8, 869-74; Bedoyan *et al* 2009 Eur J Med Genet 52, 262-4). Pilozzi-Edmonds *et al* reported a case of male dizygotic twins with an identical *de novo FGD1* mutation that resulted from germline mosaicism in the phenotypically normal mother (Pilozzi-Edmonds *et al* 2011 Am J Med Genet A 155, 1987-90).

Detection of a *FGD1* mutation depends on how well patients meet the diagnostic criteria, which is the association of three or more classical signs such as moderate short stature, hypertelorism, brachydactyly, short nose, shawl scrotum and cryptorchidism. Features of interdigital webbing, fifth finger clinodactyly, widow's peak, broad forehead, broad nasal bridge, ptosis, and wide philtrum would strengthen the diagnosis of AAS. When a mutation is not detected this is due to the clinical heterogeneity of AAS and that some of the clinical features are seen in other disorders such as Noonan syndrome, SHORT syndrome, pseudohypoparathyroidism and Robinow syndrome (Orrico *et al* 2010 Am J Med Genet 152A, 313-318).

26. Clinical validity (positive and negative predictive value in the target population)

The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical condition or predisposition. It is measured by its *positive predictive value* (the probability of getting the condition given a positive test) and *negative predictive value* (the probability of not getting the condition given a negative test).

Positive predictive value: Predictive testing would not be required for AAS as its onset is in childhood. Testing would be diagnostic even in very young children.
Negative predictive value: In a family in which the mutation is known, the value of a negative test is extremely high, effectively ruling out any likelihood of the condition. The answer is less clear for an individual with no family history. A negative genetic test would reduce the likelihood of the condition being present, but there would be a residual and currently unquantifiable risk of the condition still being present because of the possibility either of locus heterogeneity or of mutations (for example promoter or regulatory) which might escape detection.

27. Testing pathway for tests where more than one gene is to be tested

Please include your testing strategy if more than one gene will be tested and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram.

One gene only will be tested.

CLINICAL UTILITY

28. How will the test add to the management of the patient or alter clinical outcome?

Identifying a *FGD1* mutation will confirm the diagnosis of AAS. There are no specific treatments for AAS but some features (e.g. hernias and cryptorchidism) may need surgical correction. Surveys of the spine should be carried out as compression of nerve roots can occur and a psychometric assessment may be necessary for patients with learning problems and/or attention deficit and hyperactivity disorder.

29. How will the availability of this test impact on patient and family life?

Identifying a *FGD1* mutation will enable a definite diagnosis of AAS to be made, thus providing information to patients and families about the condition that is present, and enabling reproductive decisions to be more easily made as the assessment of recurrence risk for future pregnancies will be possible. Carrier testing for other female relatives will also be possible. Prenatal diagnosis can be offered once a pathogenic *FGD1* mutation has been identified. However it may not be requested since clinical features in affected males can be mild and variable. The prediction of the resulting phenotype in a fetus with a *FGD1* mutation can be difficult (Shalev *et al* 2006 Am J Med Genet 140, 1331-1332).

30. Benefits of the test Please provide a summary of the overall benefits of this test.

See section 28 and 29.

31. Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test), please state the added advantage of the molecular test.

No.

32. Please describe any specific ethical, legal or social issues with this particular test.

There are none which relate particularly to this test.

33. The Testing Criteria must be completed where Testing Criteria are not already available.

If Testing Criteria are available, do you agree with them Yes/No

If No:

Please propose alternative Testing Criteria AND please explain here the reasons for the changes.

Not applicable.

34. Savings or investment per annum in the diagnostic pathway based on national expected activity, cost of diagnostics avoided and cost of genetic test. Please show calculations.

Without molecular testing the diagnosis of AAS is based on clinical evaluation and it is often not possible to make it definitively in an isolated case. In some cases a skeletal survey may be performed to look for skeletal features related to short stature conditions. It is difficult to argue that cost savings derive from making the test through molecular genetic means rather than through a different modality such as imaging or biochemistry, because other modalities are not available to make a definite diagnosis. However, it is important to stress that for the *family*, the provision of diagnostic certainty is of potentially enormous benefit, and this can enable reproductive decisions to be made.

35. List the diagnostic tests/procedures that would no longer be required with costs.

Costs and type of imaging procedures	£143.90 (skeletal survey)
Costs and types of laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
Costs and types of physiological tests (e.g. ECG)	
Cost and types of other investigations/procedures (e.g. biopsy)	
Total cost tests/procedures no longer required	**£143.90**

36. REAL LIFE CASE STUDY

In collaboration with the clinical lead, describe a real case example to illustrate how the test would improve patient experience.

A 2 week old baby was referred with short stature and dysmorphic features. His parents were understandably very concerned about what the cause may be and his prognosis. In addition they had stored embryos (from donor egg) which they wished to use in the very near future (due to the mother's age). They did not feel able to go ahead with another pregnancy without a diagnosis in their son and accurate information about the chance of a subsequent baby having the same syndrome. The paediatricians had already tested for achondroplasia and hypochondroplasia. We arranged array CGH to exclude a chromosomal rearrangement as although AAS was a strong possibility testing was not available in the UK at the time. As these investigations were normal we arranged *FGD1* analysis in Italy. This confirmed the clinical suspicion of AAS. This result enabled the family to make a fully informed decision about their reproductive options. It was also very reassuring for them as AAS is rarely associated with significant learning difficulties. It also meant we did not need to arrange as many follow up appointments or a skeletal survey as the diagnosis was certain.

37. For the case example, if there are cost savings, please provide these below:

PRE GENETIC TEST

Costs and type of imaging procedures	£143.90 (skeletal survey)
Costs and type of laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
Costs and type of physiological tests (e.g. ECG)	
Cost and type of other investigations/procedures (e.g. biopsy)	
Cost outpatient consultations (genetics and non genetics)	
Total cost pre genetic test	**£**

POST GENETIC TEST

Costs and type of imaging procedures	
Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
Cost of genetic test proposing in this gene dossier	£600
Costs and type of physiological tests (e.g. ECG)	
Cost and type of other investigations/procedures (e.g. biopsy)	
Cost outpatient consultations (genetics and non genetics)	Reduced appointments (see section 38)
Total cost post genetic test	**£**

38. Estimated savings for case example described £

There may be no direct cost savings in making the diagnosis for reasons stated in section 34, above. It is possible fewer genetic appointments will be needed once the diagnosis is confirmed. Where molecular information is used in reproductive decision-making, through pre-natal diagnosis (or in the case above the decision not to use the stored embryos), significant distress to both parents and child is avoided if a pregnancy which is predicted to be affected is terminated.

UKGTN Testing Criteria

Approved name and symbol of disease/condition(s):	**OMIM number(s):**
Aarskog-Scott Syndrome; AAS	305400
Approved name and symbol of gene(s):	**OMIM number(s):**
fyve, rhogef, and ph domain-containing 1; FGD1	300546

Patient name:	**Date of birth:**
Patient postcode:	**NHS number:**
Name of referrer:	
Title/Position:	**Lab ID:**

Referrals will only be accepted from one of the following:	
Referrer	**Tick if this refers to you.**
Consultant clinical geneticist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Three or more signs from: • moderate short stature, • distinct craniofacial abnormalities, (including hypertelorism, down-slanting palpebral fissures and short nose with upturned nares), • short and characteristic hands (brachydactyly with inter digital webbing) • shawl scrotum • cryptorchidism • hypermetropia	
At risk family members where familial mutation is known	

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample