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

Test – Disease – Population Triad

Disease – name and description (please provide any alternative names you wish listed) (A)-Testing Criteria	Fibrodysplasia Ossificans Progresiva (FOP)
OMIM number for disease	#135100
Gene – name and description (please provide any alternative names you wish listed)	Activin A, type I receptor (ACVRI)
OMIM number for Gene	*102576
Mutational spectrum for which you test	Specific mutation c.617G>A
Technical Method (s)	PCR of the region and restriction digest
Validation Process **Note please explain how this test has been validated for use in your laboratory)**	Stored DNA from 6 known affected patients, 1 atypical patient and 10 normal controls were tested using the chosen method. Mutations were found in all 6 FOP patients but none were found in the atypical and the normal controls. Numbers limited due to the rarity of the disorder. The test is simple and well established in the laboratory.
Are you providing this test already? If yes, how many reports have you produced? **NB please give the number of mutation positive/negative samples you have reported**	Yes. 5 referrals reported so far. 3 carried the mutation; 2 did not.
For how long have you been providing this service?	6 months
Is there specialised local clinical/research expertise for this disease?	**Yes X** | **No** | **Please provide details** Professor Connor has a long term research interest in this disorder and is an international authority on the condition.
Are you testing for other genes/diseases closely allied to this one? Please give details	**No**
Your Activity How many tests do you (intend to) provide annually in your laboratory?	**20**

Based on experience how many tests will be required nationally? Please identify the information on which this is based	~10 a year once known patients have been tested. Possibly a further 20 from Europe.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	40 –50 patients known in the UK 1 in 1-2 million
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Shore,E.M. *et al* including J.M. Connor A recurrent mutation in the BMP type I receptor ACVRI causes inherited and sporadic fibrodysplasia ossificans progressive. Nature Genetics, 38,525-527, 2006. Little hard evidence yet for this rare disease.
Estimated penetrance Please identify the information on which this is based	Fully penetrant
Target Population The essential clinical or family history features defining the target population must be described. (C)-Testing Criteria	FOP patients have typical malformationsof the great toes in most cases and develop disabling ectopic bone. This test helps to confirm a suspected diagnosis in a young child with suggestive malformations but before the formation of ectopic bone.
Estimated prevalence of disease in the target population	**>95%**

Intended Use (Please use the questions in Annex A to inform your answers)

Please tick the relevant clinical management criteria that this test effects.	YES	NO
Diagnosis	X	
Treatment		X
Prognosis & Management	X	
Presymptomatic testing	X	
Risk Assessment	X	

Test Characteristics

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.	Analytical sensitivity is approaching 100%. Primers are regularly checked for SNPs which would be the single likeliest source of any error. The specificity of the test for the c.617G > A mutation is 100%
Clinical sensitivity and specificity of test in target population The *clinical sensitivity* of a test is the probability of a positive test result when disease 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 disease (for specificity) *Positive predictive value* and *penetrance* are notionally equivalent for any single genetic allele – the probability of developing disease given a positive test. The relationship is much more complex if more than one gene is responsible for the disease (locus heterogeneity), or if in any one gene there are multiple alleles (allelic heterogeneity), unless all the alleles are tested. In these cases, there are implications for the *clinical sensitivity* of the test and for *its negative predictive value*. For example, for a disease (such as APKD) that may be caused by either of two separate genes, even if each is 100 percent penetrant, the *clinical sensitivity* and the *negative predictive value* (and *clinical validity*) will both be reduced: c*linical sensitivity* since its maximum value can be no greater than the	The specific mutation is seen in 100% of FOP patients with typical big toe malformations and disease. It is not seen in atypical FOP patients i.e. clinical sensitivity for typical disease is 100%

proportion of the disease that is caused by that particular gene, and *negative predictive value* since a negative test on Gene A will be no guarantee that the patient will not develop the phenotype, because the disease may be caused by Gene B. A similar form of analysis may be applied to genes with multiple alleles unless the "test" measures all the alleles	

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 disease or predisposition. It is measured by its *positive predictive value* (the probability of getting the disease given a positive test) and *negative predictive value* (the probability of not getting the disease given a negative test). The denominator in this case is the number of people with a positive or a negative test respectively - not the number with or without the disease. The clinical validity may be calculated knowing the sensitivity and the specificity and the prevalence of the disease in the population being studied. Positive and negative predictive values depend critically on the prevalence of the disease in the test population *Positive predictive value* and *penetrance* are notionally equivalent for any single genetic allele – the probability of developing disease given a positive test. The relationship is much more complex if more than one gene is responsible for the disease (locus heterogeneity), or if in any one gene there are multiple alleles (allelic heterogeneity), unless all the alleles are tested. In these cases, there are implications for the *clinical sensitivity* of the test and for *its negative predictive value*. For example, for a disease (such as APKD) that may be caused by either of two separate genes, even if each is 100 percent penetrant, the *clinical sensitivity* and the *negative predictive value* (and *clinical validity*) will both be reduced: c*linical sensitivity* since its maximum value can be no greater than the proportion of the disease that is caused by that particular gene, and *negative predictive value* since a negative test on Gene A will be no guarantee that the patient will not develop the phenotype, because the disease may be caused by Gene B. A similar form of analysis may be applied to genes with multiple alleles unless the “test” measures all the alleles.	The specific mutation has not been seen in normal individuals i.e. PPV = 100%

Clinical utility of test in target population (Please refer to Appendix A) Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing.	Currently patients with suspected FOP from around the world are directed by the IFOPA website to the nearest local expert. Examination of their history and x-rays may allow diagnosis and this test will provide unequivocal confirmation. It is expected that referral through the website will continue since the disease is so rare. Professor Connor will examine the clinical information provided to ensure the test is appropriate.
(B)-Testing Criteria	
	Avoidance of trauma in FOP patients helps to reduce the occurrence of ectopic bone formation.
How will the test add to the management of the patient or alter clinical outcome?	
	Early diagnosis prior to ectopic bone formation can allow improved management and reduction in the disabling effects. Reduction in the level of disability and the concomitant costs to the NHS in the affected individuals.
What impact will this test have on the NHS i.e. by removing the need for alternative management and/or investigations for this clinical population	
	Physical examination and examination of X-rays may allow a diagnosis but this is frequently delayed until after the formation of ectopic bone.
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	
Please complete the referral pathway diagram on the following page and the testing criteria form.	

Referral Pathway Template –

NOTE: Please use this page as a template. Please expand the test boxes manually as needed.

TARGET

POPULATION
(Description)
Patients with a suspected diagnosis of FOP.

WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?

Clinical Geneticists

PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?

Family history of FOP **and/or** Malformation of the great toes and X-ray features of FOP

HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

20 -30

UKGTN Testing criteria

Patient name:

Patient postcode:

Name of referrer:

Title/Position:

Name of Disease/test: Fibrodysplasia Ossificans Progresiva (FOP)

Referrals will only be accepted from one of the following:
(Please indicate with a tick which category refers to the referrer).

Referrer	Tick if this refers to you.
Clinical Geneticists	
Consultant Specialists	
Named clinicians	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

Criteria	Tick if this patient meets criteria
Criteria 1 e.g. family history of X	
Criteria 2 e.g. clinical symptoms Malformationof the great toe. X-ray features of the disease	
Criteria 3 e.g. requires a particular result from a different investigation	