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

Test – Disease – Population Triad

Disease – name	Thoracic Aortic Aneurysms Dissections (TAAD)
OMIM number for disease	132900,611788
Disease – alternative names please provide any alternative names you wish listed	Aortic Aneurysm, Familial Thoracic 4, AAT4 Aortic Aneurysm, Familial Thoracic 6, AAT6 TAAD2
Disease – please provide a brief description of the disease characteristics	Cardiovascular manifestations of familial thoracic aortic aneurysms and aortic dissections (TAAD) include: (1) dilatation of the aorta at the level of either the ascending aorta or the sinuses of Valsalva; and (2) aneurysms and dissections of the thoracic aorta involving either the ascending or descending aorta. Cardiovascular manifestations are usually the only findings. Affected individuals typically have progressive enlargement of the ascending aorta leading to either aortic dissection involving the ascending aorta (type A dissection) or consequent tear or rupture. The onset and rate of progression of aortic dilatation is highly variable.
Disease - mode of inheritance	Autosomal Dominant
Gene – name(s)	MYH11, myosin, heavy chain 11, smooth muscle ACTA2 Actin,Alpha-2, Aortic Smooth Muscle
OMIM number for gene(s)	160745; 102620
Gene – alternative names please provide any alternative names you wish listed	Myosin, heavy polypeptide 11, smooth muscle Actin,Alpha-2, Aortic Smooth Muscle
Gene – description(s) (including number of amplicons).	The coding region of MYH11 at 16p13.13-p13.12 encodes the myosin, heavy chain 11, smooth muscle protein and consists of 41 exons. Two alternatively spliced transcripts SM1 and SM2 are generated by alternative usage of exon 41. The coding region of ACTA2 at 10q22-q22 encodes the smooth muscle alpha-actin protein. It is a major contractile protein in muscle, and polymerization of ACTA2 forms the backbone of the thin filament of the sarcomere. The coding region of ACTA2 consists of 9 exons.
Mutational spectrum for which you test including details of known common mutations.	Multiple point mutations across the ACTA2 and MYH11 genes. Published reports state that mutations in TGFBR1/2 are found in approx. 3.5% of individuals with familial TAAD. Missense mutations in ACTA2 account for 14% mutations in individuals with a related thoracic aortic aneurysms aortic and aortic dissections (TAAD) phenotype. Little data available for MYH11 mutations although splicing and missense mutations in patients with TAAD and patent ductus arteriosus (PDA) have been reported. Zhu et al

	Nat. Genet 2006; 38: 343-349. Pannu et al Hum Mol Genet. 2007; 16:2453-2462. Guo et al Nat Genet. 2007; 39: 1488-93.
Technical Method (s)	Mutation detection in partial intronic and all exonic fragments by PCR amplification, heteroduplex (DHPLC) and sequence analysis.
Validation Process Note: please explain how this test has been validated for use in your laboratory	The DHPLC platform has been already validated using a full range of positive controls for 35 exons of hMLH1 and hMSH2 (HNPCC) and 65 exons of FBN1(MFS). Limited positive controls are available for the exons of these gene however innate gene polymorphisms plus known commercial positive controls are incorporated on each run and evaluated to ensure constant optimum running conditions are maintained.
Are you providing this test already? If yes, how many reports have you produced? Please give the number of mutation positive/negative samples you have reported	No but we are providing a service for Marfan (FBN1) negative cases for genes causing a related phenotype. TGFBR1, of 31 reports issued, 3 were positive i.e.9.7% TGFBR2, of 88 reports issued, 6 were positive i.e. 6.8% No report data yet available for ACTA2 and MYH11 testing. Validation only, completed. Service to start Ist Sept 09
For how long have you been providing this service?	MFS service since 2002, MYH11 and ACTA2 will be new additions.
Is there specialised local clinical/research expertise for this disease?	**Yes** | **Please provide details** Marfans and related syndromes have long been a clinical specialty of the Wessex Clinical Genetics Service based at PAH, Southampton
Are you testing for other genes/diseases closely allied to this one? Please give details	Yes, TGFBR1 and TGBFR2. Four genes and 2 loci are known to be associated with TAAD: TGFBR2, TGFBR1, MYH11, ACTA2 and both loci TAAD1 and FAA1 for which the causative genes are unknown.
Your Activity If applicable - How many tests do you currently provide annually in your laboratory?	100-110 annually for TGFBR1 and TGFBR2. MYH11 and ACTA2 teting to be offered from Sept 09.
Your Activity How many tests will you be able to provide annually in your laboratory if this gene dossier is approved and recommended for NHS funding?	Index cases: 100 to 300 of FBNI, TGBR1, TGFR2 negative cases. Family members where mutation is known: 20 - 30 assuming a 10% detection rate
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	**I**ndex cases: up to 300 allowing for reduced penetrance in females and low clinical pickup. Family members where mutation is known: 60 This is on our own data and is based on the fact that Salisbury is the main UK centre for MFS and related disorders

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”.	200 - 300

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	Aortic aneurysms represent the 13th major cause of death in the United States (pop 304 million) accounting for nearly 15,000 deaths annually (equivalent to 3,000 deaths in the UK). Approximately 20% of thoracic aortic aneurysms and dissections result from a genetic predisposition. Biddinger et al J.Vasc.Surg.1997;25,506-511. Coady et al Arch.Surg.1999;134,361-367. Predisposition is not known to be increased in any ethnic or racial group.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	> 1 in 100,000 Biddinger et al J.Vasc.Surg.1997;25,506-511. Coady et al Arch.Surg.1999;134,361-367.
Estimated penetrance Please identify the information on which this is based	20% of TAAD affected individuals have a genetic predisposition for TAAD inherited primarily in a autosomal recessive manner with decreased penetrance and variable expression. Guo et al. Nat Genet. 2007; 39: 1488-93.
Target Population Description of the population to which this test will apply (i.e. description of the population as defined by the minimum criteria listed in the testing criteria)	Local and national affected individuals with a diagnosis of TAAD on the basis of the presence of dilatation and/or dissection of the thoracic aorta, absence of Marfan syndrome and other connective tissue abnormalities, and presence of a positive family history.
Estimated prevalence of disease in the target population	> 1 in 10-20,000

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

Please tick the relevant clinical purpose of testing	**YES**	**NO**
Diagnosis	✓	
Treatment	✓	
Prognosis & Management	✓	
Presymptomatic testing	✓	
Risk Assessment for family members	✓	
Risk Assessment – prenatal testing	✓	

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. If more than one gene will be tested, please include your testing strategy and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram.	Will detect > 95% of mutations in MYH11, ACTA2, TGFBR1 and TGFBR2. Testing Strategy for TAAD: 1st TGFBR1 (unknown but 10% of FBN1 negative*) 2nd TGFBR2 (unknown but 7% of FBN1 negative*) 3rd ACTA2, 14% reported detection rate for ACTA2 (Guo et al. Nat Genet. 2007; 39: 1488-93.) 4th MYH11 (unknown) *Figures based actual lab data which includes
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)	Overall unknown but probably greater than 14% clinical sensitivity on the basis of reported findings for ACTA2 alone by Guo et al. 2007.
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).	High probable predictive value although interpretation of missense mutations may be difficult but should improve as more data is generated through family studies etc.

Clinical utility of test in target population (Please refer to Appendix A) Please provide a description of the clinical care pathway.	To confirm diagnosis and guide management. To allow reliable testing of at-risk relatives and prenatal diagnosis if requested. 'Identifying specific mutation allows targeted clinical surveillance in family and preventative treatment to avoid familial sudden death, plus reassurance to those no longer at- risk' Management of aortic aneurysms requires coordinated input from a multidisciplinary team of specialists including a medical geneticist, cardiologist, and cardiothoracic surgeon. Ideally, cardiologists who are familiar with this condition should manage individuals with familial thoracic aortic aneurysm and dissection. Following initial evaluations after diagnosis which would include: (1) echocardiography to assess the aortic root diameter and the structure and competence of the aortic valve. Imaging of the entire aorta should be considered, as aneurysms in other portions of the aorta may be common. (2) Imaging of the vasculature, including the cerebral circulation, in individuals with TGFBR2 mutations. (3) Assessment for inguinal hernias by examination Clinical assessment for scoliosis, with follow-up X-rays if it is clinically suspected. (4) Ocular and physical examination to exclude the diagnosis of Marfan syndrome. Echocardiography surveillance would then be performed at frequent intervals to monitor status of the ascending aorta.
How will the test add to the management of the patient or alter clinical outcome?	Helpful in this group to have a precise diagnosis. Informs cardiovascular specialities to maintain echocardiography surveillance of mutation carriers whilst removing low risk non carriers from the surveillance programme. Similarly will help identify some asymptomatic relatives for surveillance and demonstrate that others are at no increased risk. Ocular and physical examination would also be carried out initially to exclude a diagnosis of Marfan syndrome
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?	A positive result could remove the need for further clinical investigation and help focus surveillance to frequent echocardiogram monitoring of the ascending aorta with follow-up prophylactic surgical repair of the aorta if necessary

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	Prior to the genetic test this was a clinical diagnosis, the molecular test greatly improves specificity. The clinical diagnosis is often inconclusive.
Please describe any specific ethical, legal or social issues with this particular test?	No

Please complete the testing criteria form.

UKGTN Testing criteria

Name of Disease(s): AORTIC ANEURYSM, FAMILIAL THORACIC 4; AAT4 (132900)
AORTIC ANEURYSM, FAMILIAL THORACIC 6; AAT6 (611788)

Name of gene(s): myosin, heavy chain 11, smooth muscle MYH11 (160745)
actin, alpha 2, smooth muscle, aorta; ACTA2 (102620)

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.
Clinical Geneticists	
Cardiologist in liason with clinical geneticist	

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

Criteria	Tick if this patient meets criteria
1. Dilatation and/or dissection of the ascending thoracic aorta, **OR** dissection of the descending aorta just distal to the origin of the subclavian artery.	
AND 2. Family history of TAAD	
AND Exclusion of Marfan Syndrome, Loeys-Dietz aortic syndrome, and other connective tissue abnormalities	
OR Family History of known ACTA2/MYH11 mutation	

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.