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

Test – Disease – Population Triad

Disease – name	Porencephaly, Familial (175780)
OMIM number for disease	175780
Disease – alternative names please provide any alternative names you wish listed	Familial Porencephaly
Disease – please provide a brief description of the disease characteristics	*COL4A1* mutations cause a spectrum of phenotypes. These include; porencephaly causing hemiplegia, hydrocephalus, epilepsy, mental retardation with poor/absent speech, dystonia and optic and pituitary defects; Leukoencephalopathy, retinal arteriolar tortuosity, renal cysts, intracerebral aneurysn, intracerebral haemorrhage and migraine.
Disease - mode of inheritance	Autosomal dominant
Gene – name(s)	*COL4A1*
OMIM number for gene(s)	120130
Gene – alternative names please provide any alternative names you wish listed	Collagen Of Basement Membrane, Alpha-1 Chain Arresten
Gene – description(s) (including number of amplicons).	*COL4A1*; location 13q34, 52 coding exons (42 amplicons)
Mutational spectrum for which you test including details of known common mutations.	Missense, nonsense, splicing and small insertion/deletion mutations. Mutations primarily affect glycines within the Gly-X-Y- repeats in the triple helix domain.
Technical Method (s)	Sequencing of exons 1-52 and conserved splice sites.
Validation Process Note: please explain how this test has been validated for use in your laboratory	*COL4A1* sequence analysis was carried out using DNA from a patient with a diagnosis of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) syndrome and a *NOTCH3* mutation.
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	Yes. Two reports issued to date.
For how long have you been providing this service?	Since August 2008

Is there specialised local clinical/research expertise for this disease?		**No**	**Please provide details**
Are you testing for other genes/diseases closely allied to this one? Please give details	Yes, CADASIL (*NOTCH3* gene)		
Your Activity If applicable - How many tests do you currently provide annually in your laboratory?	Index cases: 2 Family members where mutation is known: 0		
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: As required Family members where mutation is known: As required		
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	Index cases: <5 tests. Family members where mutation is known: <5		
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".	Not applicable		

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	No epidemiological data are available This is a rare syndrome and no accurate estimates of prevalence have been published.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Unknown
Estimated penetrance Please identify the information on which this is based	Testing of 9 individuals in three Dutch families affected with porencephaly identified the familial mutation in all individuals and was not detected in 6 unaffected family members (Breedveld *et al*. J. Med. Genet. 2006;43:490-495). Testing of 9 individuals in 3 families with HANAC syndrome identified the familial mutation in all 9 individuals and not in 10 unaffected family members (Plaisier *et al* N. Eng. J. Med. 2007; 357:2687-95). Gould *et al* reported a family with cerebral haemorrhage where all affected individuals (n=6) carry the familial mutation (Gould *et al* N. Eng. J. Med.2006:354:1489-96).
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)	Testing will be available for all patients with evidence of familial porencephaly or family history of porencephaly. Family members of individuals with an identified *COL4A1* mutation.
Estimated prevalence of disease in the target population	Unknown

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.	Single direction sequence analysis using Mutation Surveyor software. Sensitivity 99% and specificity 99% (in-house data)
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)	Clinical sensitivity is affected by the variable phenotype and age of onset. Not all mutation carriers have infantile porencepahly and hemiparesis, but have migraine or cerebral haemorrhage in adulthood. Sporadic cases of early onset cerebral haemorrhage due to *COL4A1* mutations have been reported (Vahedi *et al*. Stroke 2007:38:1461-64).
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 presence of a COL4A1 mutation does not predict the likely severity of the phenotype. Intra-familial variation has been reported and suggests environmental factors such as birth trauma, anticoagulant use and head trauma Influence the phenotype.

Clinical utility of test in target population (Please refer to Appendix A) Please provide a description of the clinical care pathway.	Molecular analysis of the *COL4A1* gene in individuals with familial porencephaly or family history of porencephaly will allow a definitive diagnosis. A molecular diagnosis will provide means by which testing can be offered to relatives and offspring at risk. A molecular diagnosis will also allow the option for prenatal diagnosis.
How will the test add to the management of the patient or alter clinical outcome?	Identification of a pathogenic mutation will provide information for the management of at risk pregnant women where caesarean section is recommended to prevent vascular injury caused by birth trauma and in at risk adults where sustained physical activity that may cause head trauma can be avoided and anticoagulant use can be strictly monitored.
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?	Mutation-negative family members will not have to be strictly managed during childbirth, physical activity and on anticoagulants.
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	Although porencepahly and cerebral haemorrhage can be seen on MRI and retinal arteriolar tortuosity on eye examination this does not identify underlying cause. It is not possible to diagnose this disorder by biochemical testing, therefore a definitive diagnosis relies on molecular genetic testing.
Please describe any specific ethical, legal or social issues with this particular test?	Not applicable

Please complete the testing criteria form.

UKGTN Testing criteria

Name of Disease(s): PORENCEPHALY, FAMILIAL (175780)
Name of gene(s): collagen, type IV, alpha 1; COL4A1 (120130)

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
Evidence for Familial porencephaly **OR**	
Close family history of Familial Porencephaly **OR**	
Relatives of affected individuals with a *COL4A1* 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.