NHS

UK Genetic Testing Network

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

Administrative Details

Test – Disease – Population Triad

Disease – name and description (please provide any alternative names you wish listed)	Cerebral Cavernous Malformations (CCM)
OMIM number for disease	116860
Gene – name and description (please provide any alternative names you wish listed)	CCM1 (KRIT1) OMIM: 604214 CCM2 (Malcavernin) OMIM: 603284 CCM3 OMIM: 603285
Mutational spectrum for which you test	Full screen for point mutations within the above genes Large-scale deletions and duplications of above genes
Technical Method (s)	B-directional sequence analysis of KRIT1, CCM2 and CCM3 Deletions/duplications detected by MLPA.
Validation Process **Note please explain how this test has been validated for use in your laboratory)**	Analysis of 26 patients with confirmed CCM. Screening of all three CCM genes for mutations.
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 Analysis has been completed for all 26 patients, although additional DNA has been requested for 3. 11 mutations identified in KRIT1 5 mutations identified in CCM2 4 mutations identified in CCM3. 3 patients negative for all three genes.
For how long have you been providing this service?	**6 months**
Is there specialised local clinical/research expertise for this disease?	**Yes** | **Please provide details** Dr X has a longstanding research interest in hereditary vascular dysplasias and currently runs specialist genetic clinics in Dundee and Guy's Hospital, London.
Are you testing for other genes/diseases closely allied to this one? Please give details	**No**

Local Activity How many tests do you intend to provide annually in your laboratory?	20-30 screens for new mutations Additional presymptomatic tests
National Activity How many tests are being provided nationally?	To our knowledge, our lab is the only laboratory in the UK currently offering a service for CCM.
Based on experience how many tests will be required nationally? Please identify the information on which this is based	20-30 new tests per annum is based on the current rate of referral of samples

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	There is little data available to give an accurate estimate of the prevalence of familial CCMs in the UK population. Taking data from the Scottish Intracranial Malformations study that endeavoured to detect all intracranial vascular malformations detected in Scotland over a 5 year period, 46 patients were identified in the first 2 years. 4 of these patients (8.7%) had multiple lesions and would therefore be expected to have a causative gene mutation. Studies in other (USA based) populations have estimated that between 0.5% (Robinson et al. J. Neurosurg 1991;75:709-14) and 0.6% of patients have at least 1 CCM on MRI scanning (Kim et al. Surgical Neurology 1997;48:9-17). An estimate derived from these studies, assuming 8.7% of all individuals with a CCM carried a mutation would suggest that approximately 1/2500 individuals carry a mutation (of the same order as Neurofibromatosis type 1). This estimate would seem high, and does not reflect current genetic practice. However these data suggest that a significant proportion of the population carry familial CCM mutations, although only a percentage of these will be symptomatic.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	From the above, up to 1/2500 individuals may carry a mutation in the CCM1, CCM2 or CCM3 gene.
Estimated penetrance Please identify the information on which this is based	The only convincing data on which to base this is the study of individuals with CCM1 mutations carried out by Denier et al. Annals of Neurology 2003;213-220. In this study 126/202 individuals (non-probands) with a CCM1 mutation were symptomatic, 71 had no symptoms but detectable lesions in scan and 5 were non-penetrant. The penetrance will be different for mutations in other genes, but there is no published data to inform this.

Target Population Please provide details on which population the test is going to be used. For example a description of the particular patient group (see Note 1 below).	This test would only be available to individuals fulfilling diagnostic criteria for hereditary CCM or as a presymptomatic test in families where a mutation is identified. We suggest the following diagnostic criteria, which are based on current clinical practice, there are no internationally defined criteria to date. Patients should fulfil one of the following 3 categories: ✓ Radiological evidence of multiple CCMs ✓ Single CCM with confirmed family history ✓ Single CCM with associated skin and eye signs o Classical retinal angiomas o Hyperkeratotic capilliary venous malformations o Rubbery subcutaneous lump with capillary malformation over the surface (these ar not pathologically defined but are seen in patients)
Estimated prevalence of disease in the target population	From our initial pilot study of 23 patients fulfilling the above criteria, a mutation was detected in 87%.

Note 1- The characteristics of the population for the test should be stated. Features such as ethnicity, age range, and affected families are all appropriate examples of population characteristics. The concept of a "test" includes the population in which it is to be applied, so, for example, a test for the Huntington gene evaluated for use in asymptomatic family members would receive a separate evaluation if it were additionally proposed that it should be used in the general population.

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	$^{D}_{4}$	
Treatment	$^{D}_{4}$	
Prognosis & Management	$^{D}_{4}$	
Presymptomatic testing	$^{D}_{4}$	
Risk Assessment	$^{D}_{4}$	

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.	Bi-directional sequencing coupled with Mutation Surveyor software has a quoted sensitivity of >99%. The sensitivity of detecting a deletion/duplication of the CCM genes by MLPA is >95%. The specificity of both techniques is >99%

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 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	In our pilot of 23 patients, with analysis of all three CCM genes, we have identified 11 mutations in KRIT1, 5 mutations in CCM2 and 4 in CCM3. Clinical sensitivity from our data is therefore 87% for combined analysis of all three CCM genes. Even if an individual is asymptomatic, testing will be relevant for reasons of genetic counselling and screening of relatives. Clinical specificity is expected to approach 100% - although genetic variants of uncertain clinical significance may be encountered during testing of affected or unaffected individuals.

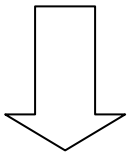
Clinical validity (positive and negative predictive value in the target population) The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical disease or predisposition. It is measured by its *positive predictive value* (the 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.	From the data given above, positive predictive value will be 63% for symptomatic lesions, but 98% for symptomatic or radiologically detectable lesions.

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 is required to illustrate the clinical utility of the test (a template is provided on page 8).	Please refer to flowchart on the next page.
How will the test add to the management of the patient or alter clinical outcome?	The finding of a pathogenic mutation in one of the CCM genes confirms a clinical diagnosis of familial CCM. Pre-symptomatic testing can then be offered to at-risk family members. It is common for family members to request brain MRI scans where there is a possible diagnosis of familial CCM. While identification of a lesion does not usually lead to a neurosurgical intervention, it can be important in informing patients of the neurological risks they face and their reproductive risks.
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	Non-identification of a lesion on MRI does not exclude the diagnosis as effectively as mutation analysis, and MRI scans may need to be repeated after a time interval, if a patient develops further concerns or vague symptoms. A patient with unusual MRI findings may avoid other unnecessary investigations if they can be safely attributed to a familial CCM mutation.
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	In a small proportion of cases mutation analysis provides essential information for parents, for example where a young child has been severely affected and there is considerable anxiety for risks to future children. Individuals may also consider prenatal diagnosis. Therefore, testing for familial CCMs would be expected to reduce the need for MRI scans in family members, make prenatal diagnosis available to patients if they wished and allow clinical genetics to inform patients more effectively of their risks and the risks to their children. Data generated from the service application would be audited, and may enable improved targeting of gene testing, determined by the clinical presentation, and improved understanding of the prognostic implications of test results.
Please complete the referral pathway diagram on the following page. Include a testing criteria form that may be available to clinicians when assessing merit of testing where possible.	

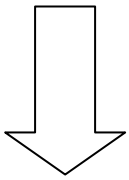
Referral Pathway Template –

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

Individuals with a diagnosed CCM and established family history of CCM
Individuals with multiple CCMs
Individuals with CCM with associated eye and/or skin signs.

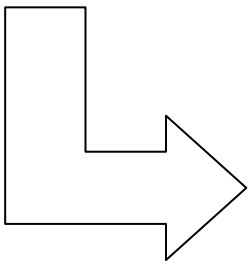


Samples accepted from genetics centres, neurologists and neurosurgeons, accompanied by adequate clinical data to ensure compliance with testing criteria



Does patient have multiple, radiologically confirmed cerebral cavernous malformations (CCM) [ ]
Does patient have a radiologically confirmed CCM with a confirmed family history of CCM [ ]
Does patient have a radiologically confirmed CCM with associated skin or eye signs [ ]

Ticking of one box would indicate a high likelihood of familial CCMs



HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

Up to 40

Testing criteria for Cerebral Cavernous Malformations

Patient name:
Patient postcode:

Name of Referring Clinician:

Title/Position:

Name of Disease/test: Cerebral Cavernous Malformations / CCM1 (KRIT1), CCM2 (Malcavernin) & CCM3 testing

Referrals only will be accepted from one of the following:

Referring Clinician	Tick if this refers to you.
Clinical Geneticists	
Neurologists	
Neurosurgeons	

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

Criteria	Tick if this patient meets criteria
Radiological evidence of multiple CCMs **or**	
Single CCM with confirmed family history **or**	
Single CCM with associated skin and eye signs: • Classical retinal angiomas • Hyperkeratotic capilliary venous malformations • Rubbery subcutaneous lump with capillary malformation over the surface	

If the sample does not fulfil these criteria and you still feel that testing should be performed you may contact the laboratory to discuss testing.