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)	Charcot Marie Tooth Type 2A classified within Hereditary Sensory and Motor Neuropathy Type 2 (axonal) CMT2A is an autosomal dominant inherited neuropathy. Clinically patients have typical distal weakness and wasting. Electrophysiology and nerve biopsy show axonal degeneration.		
OMIM number for disease	609260		
Gene – name and description (please provide any alternative names you wish listed)	MFN2		
OMIM number for Gene	608507		
Mutational spectrum for which you test	Point mutations and small insertions/deletions. These are the only mutations reported to date.		
Technical Method (s)	High Throughput Automated sequence analysis.		
Validation Process **Note please explain how this test has been validated for use in your laboratory)**	HT automated sequence analysis (ABI 3730XL/ SeqScape) is the screening technology in routine use. Primers (SNP checked) have been designed to cover all coding regions. Compare sequence obtained with NCBI reference sequence data.		
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**	Providing already 150 reports to date.		
For how long have you been providing this service?	Since March 2006.		
Is there specialised local clinical/research expertise for this disease?	**Yes**		**Please provide details**
	ION and BGL clinical and laboratory collaboration. Previous joint gene dossiers submitted in this area. Currently the two laboratories work in a collaborative way to provide specialist UKGTN peripheral neuropathy services. Both centres are members of the European CMT consortium and have participated in European and National meetings. ION has a strong research backgroud in the Peripheral neuropathies. Dr Mary Reilly (ION) in collaboration with Professor Francesco Muntoni run UK specialist adult and paediatric peripheral nerve clinics.		

	Dr Reilly is the vice chairman of the British Peripheral Nerve Society (BPNS) and in this position is in close contact with all her colleagues in the UK interested in peripheral neuropathies. Dr Peter Lunt (Bristol) is a Clinical Geneticist with special interest in muscle and nerve disease.
Are you testing for other genes/diseases closely allied to this one? Please give details	ION is the London centre for peripheral neuropathy services. UKGTN service provision for; PMP22 (601097) MPZ (159440) GJB1(Cx32) (304040) SPTLC1 (605712) GDAP1 (606598) BSCL2 (606158)
Your Activity How many tests do you (intend to) provide annually in your laboratory?	Approximately 100
Based on experience how many tests will be required nationally? Please identify the information on which this is based	We estimate a large demand for these tests as the incidence of hereditary neuropathies in total is >1/2,500. Of these, approx. 25% are of axonal type (HMSN2), suggesting an incidence of HMSN2 as ~ 1/10,000. With 6000 patients in the UK, we anticipate between 50-100 requests nationally per year.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	The prevalence of CMT is 1/2500 CMT2 accounts for 24% of cases[1] There is only one common genetic cause of CMT2 (mutations in Mitofusin 2) causing about 20% of all autosomal dominant forms of CMT2[2]. Unfortunately there are no other common causes of A.Dom or A.Rec CMT or related hereditary peripheral neuropathies, with 26 causative genes having already been identified. Most of these genes have only been described in a limited number of cases and indeed some of the genes have only been described in individual families. The estimated prevalence of these rare inherited neuropathies in England is between 1.6 and 2.5/100,000 (800 to 1250 patients in England). 1 Harding and Thomas, Brain 103: 259-280; 1980 2 Stephan Züchner et al, Nature Genetics 36, 449-451 2004
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Unknown in the UK – if heterozygote freqy. is presumed to be around 20% x 1/10,000 , then gene frequency will be ~ 1/100,000
Estimated penetrance Please identify the information on which this is based	Assumed to be close to 100% - this may change with number of cases analysed.
Target Population The essential clinical or family history features defining the target population must be described.	1. CMT2 (nerve conduction velocity > 38 m/sec). ***and*** 2. Isolated case or pedigree suggestive for autosomal dominant inheritance ***and*** 3. Referred by a paediatric or adult neurologist /neuromuscular specialist, or clinical geneticist.
Estimated prevalence of disease in the target population	Up to 20%

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	√	
Treatment		√ Specific drug treatment for CMT not available at present but may change in the future.
Prognosis & Management	√	
Presymptomatic testing	√ (in infancy)	
Risk Assessment	√ (prenatal diagnosis)	

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.	HT Automated Sequence analysis. Sensitivity 99-100%. To our knowledge currently no variant has been missed using a bi-directional sequencing approach. Current validation of unidirectional sequencing within coding region indicates a sensitivity of 99%. Specificity 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	**Sensitivity:** 99% **Positive predictive value / penetrance :** Presumed 100%. **Specificity :** Presumed over 90 %.

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	
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.	**Positive Predictive Value** : Close to 100% **Negative Predictive Value :** Estimated 98-99 %

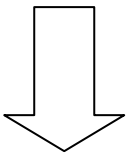
Clinical utility of test in target population (Please refer to Appendix A) Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing. (B)-Testing Criteria How will the test add to the management of the patient or alter clinical outcome? 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 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.**	1. Affected patients or families will already have been categorised as having axonal neuropathy from nerve conduction testing. The majority of female patients referred for testing will be expected already to have undergone analysis of GJB1. 2. Samples can be accepted from paediatric and adult neurologists or from clinical geneticists, but should be accompanied by appropriate clinical information, for review by agreed appropriate designated clinical expertise, to discuss in each case the optimal path of rare gene analysis should the MFN2 result prove to be negative. This will be provided from the National Hospital for Neurology, the Hammersmith Hospital, and Bristol. 3. A proportion of samples are expected through a planned BGL/ION care pathway for the rare peripheral neuropathies, but where MFN2 has not yet been tested. i.e. i) Specialist clinics for adult patients (>16yrs) in the National Hospital for Neurology are coordinated by Dr Reilly. For children (<16yrs) a similar service is co-ordinated by Professor Muntoni in the Hammersmith hospital . There is also a joint Reilly/Muntoni clinic also in the Hammersmith hospital. Clinical consultation, neurophysiology and if necessary a nerve biopsy and therapy opinion can be offered. In particular these clinics offer not only a diagnostic opinion, but also associated physiotherapy, OT, orthotic, and other management advice. or ii) Clinicians may request advice from ION or Bristol on how to take the genetic diagnosis forward by letter or email enclosing all the clinical details and the neurophysiology and if appropriate the blocks of the nerve biopsy for further analysis. This test will usually be the first one in a strategy of specialist tests for rare peripheral neuropathies which could be requested in light of clinical information. Clinical testing criteria will be as indicated (earlier) for the defined target population : 1. CMT2 (nerve conduction velocity > 38 m/sec). ***and*** 2. Isolated case or pedigree suggestive for autosomal dominant inheritance ***and*** 3. Referred by a paediatric or adult neurologist /neuromuscular specialist, or clinical geneticist. <u>Testing will be offered where it may :</u> 1. Confirm diagnosis 2. Enable prognostic prediction and appropriate planning of clinical and lifestyle management. 3. Establish inheritance pattern (as autosomal dominant, and

	hence provide accurate advice on genetic risk) 4. Enable prenatal diagnosis where this is requested 5. Enable accurate carrier testing in families with multiple consanguinity. <u>Impact on NHS</u> A molecular diagnosis may avoid the need for nerve biopsy if the clinical and neurophysiological investigation is, together with family history, sufficiently suggestive of CMT2. In families choosing prenatal diagnosis, the testing may avoid a repeat of long-term service demands on the NHS. There is no definitive alternative diagnostic means, as even the characteristic nerve pathology does not confirm the recessive inheritance pattern. There are no alternative biochemical tests. Genetic analysis is key to appropriate classification and management of the peripheral neuropathies. <u>Clinical Utility</u> : as above, this will be for : Diagnosis : Prognostic prediction Establishing or confirming inheritance pattern Risk prediction – and particularly for prenatal diagnosis Future potential for treatments.

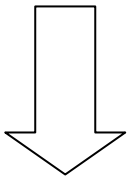
Referral Pathway Template –

Referral criteria

1. CMT2 (nerve conduction velocity > 38 m/sec) Electrophysiology and nerve biopsy show axonal degeneration.
2. Isolated case or pedigree suggestive for autosomal dominant inheritance

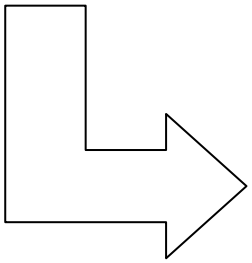


WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?
Clinical Geneticists and Adult and Paediatric Neurologists following discussion with relevant designated expertise : e.g. at Institute of Neurology (ION), Hammersmith or Bristol



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

Clinical presentation criteria to be met.
Appropriate Genetic Testing strategy for Peripheral Neuropathy genes to be devised for each case by expertise from the testing organisation.
Broadly this will follow the analysis path guidelines in the enclosed article (Reilly M. *Practical Neurology* 2007;7;93-105)



HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

Approximately 100

UKGTN Testing criteria

Patient name:

Patient postcode:

Name of referrer:

Title/Position:

Name of Disease/test:
Charcot Marie Tooth Disease, Axonal, type 2A
Mitofusin (MFN2)

Referrals will only be accepted from one of the following:

Referrer	Tick if this refers to you.
Clinical Geneticists	
Specialist Neurologists	

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

Criteria	Tick if this patient meets criteria
CMT2 (Axonal peripheral neuropathy with nerve conduction velocity > 38 m/sec) **AND**	
Isolated case or pedigree suggestive of autosomal dominant inheritance	