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 CMT2K - Heterogeneous phenotype CMT2K is autosomal dominant or autosomal recessive - Usually axonal, but can be intermediate /demyelinating (see CMT 4A) - May have associated vocal cord paresis		
OMIM number for disease	609260		
Gene – name and description (please provide any alternative names you wish listed)	GANGLIOSIDE-INDUCEDDIFFERENTIATION-ASSOCIATED PROTEIN 1 **(**GDAP1)		
OMIM number for Gene	606598		
Mutational spectrum for which you test	Point mutations and small insertions/deletions.		
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. Sequences are compared with NCBI 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 11 reports to date		
For how long have you been providing this service?	Since April 2007.		
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) MFN2 (609260) BSCL2 (606158) GDAP1 (214400)
Your Activity How many tests do you (intend to) provide annually in your laboratory?	30 -40
Based on experience how many tests will be required nationally? Please identify the information on which this is based	30-40 Prevalence of rare CMT cases is 1.6-2.5/100,000 which is 900 to 1500 patients in the UK. Samples will have been tested for other genes that more commonly cause CMT1/CMT2

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	**In the UK** CMT has been estimated to affect 6-9 per 100,000 of the population [1-7]. Varying frequencies (up to 28/100,000) have been described in other populations, the discrepancies explained in part by different rates of consanguinity. **Eg. Prevalence in US (Figures from St Louis NM Disease Centre)** • Hereditary neuropathies: ~30 per 100,000 • CMT Type 1: 15 per 100,000 • CMT 1A: 10.5 per 100,000 • CMT 2: ? 7 per 100,000 In the UK, CMT1 (76%) s also more common than CMT2 (24%)[6]. For CMT1, 70% of CMT1 is due to PMP22 gene duplication on chromosome 17, and follows autosomal dominant inheritance. The next most common forms of CMT1 are due to mutation in Connexin 32 (GJB1) (X-linked partial dominant), and dominant point mutations in PMP22 and myelin protein zero gene (MPZ), causing CMT1B. Screening of these 3 genes identifies the genetic cause of CMT1 in over 90% of cases. Hence, a maximum prevalence for any of the rarer forms of CMT1 would be : < 1.5 / 100,000. There is only one common genetic cause of CMT2 (mutations in Mitofusin 2) causing about 20% of all autosomal dominant forms of CMT2[10]. 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 Davis *et al*. J Gen Hum 26: 311-349; 1978. 2 Brooks *et al*. J Med Genet 19: 88-93; 1982. 3 MacMillan *et al*. Clin Genet 45: 128-134; 1994. 4 MacDonald *et al*. Brain 123: 665-676; 2000. 5 Dyck *et al*. Ann Neurol 10: 222-226; 1981. 6 Harding and Thomas. Brain 103: 259-280; 1980. 7. Szigeti *et al*. Genetics in Medicine 8: 86-92; 2006.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Unknown in the UK
Estimated penetrance Please identify the information on which this is based	Assumed to be close to 100% (Mary Reilly pers comm.).
Target Population The essential clinical or family history features defining the target population must be described.	Individuals with demyelinating/axonal/intermediate CMT and recessive/dominant/sporadic inheritance that do not have mutations in other genes that cause CMT
Estimated prevalence of disease in the target population	Not known in the UK; no accurate data available. For CMT2, after exclusion of MFN2, the prevalence of all forms will be approx. 5 /100,000. For rarer Dominant mutations, this suggests a maximum gene frequency of < 2.5 /100,000 (heterozygote freqy. of < 5/100,000) . For recessive axonal forms, the maximum prevalence will also be < 5/100,000; and a maximum gene frequency therefore 1/150 (max. carrier freqy < 1/75). However, for most of these the individual gene frequencies are likely to be much lower.

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; carrier testing in consanguineous families)	

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 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	**Sensitivity:** 99% **Positive predictive value / penetrance :** Presumed 100%. **Specificity :** Presumed over 90 %.

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	

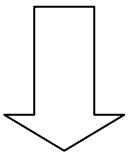
Clinical validity (positive and negative predictive value in the target population) The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical disease or predisposition. It is measured by its *positive predictive value* (the 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. The majority of patients referred for testing will already have been analysed for other genes that could cause CMT2 [MPZ, GJB1 (in females), MFN2], or intermediate presentation [above plus PMP22 (mutation and dosage) and all GJB1]. 2. Samples can be accepted from paediatric and adult neurologists or from clinical geneticists, but only accompanied by appropriate clinical information, and after review of this by agreed appropriate designated clinical expertise to discuss in each case the optimal path of rare gene analysis. This will be provided from the National Hospital for Neurology, the Hammersmith Hospital, and Bristol. 3. Most samples are expected through a planned BGL/ION care pathway for the rare peripheral neuropathies. **ie. 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)** A second referral pathway will operate where the clinician requests 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 be one in a strategy of specialist tests for rare peripheral neuropathies which could be requested in light of clinical information. All of the genetic analysis would be carried out in the laboratories in the National Hospital for Neurology (Dr Reilly and Dr Davis) and Bristol (M.Williams). The tests for rare genes will be organised in such a way to avoid duplication between the two laboratories. We feel that it is crucial for all genetic testing to be undertaken only after a clinical opinion by one of the two mechanisms above to avoid unnecessary and inappropriate requests. Clinical testing criteria will be as indicated (earlier) for the defined target population: <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.

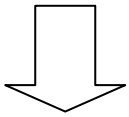
Referral Pathway Template –

1. Individuals with axonal / or intermediate demyelinating CMT and dominant /sporadic or recessive inheritance that do not have mutations in other genes that cause axonal CMT [ie. MPZ, GJB1 (in women), or MFN2] , or intermediate demyelinating CMT [ie. GJB1, PMP22 del/dup or mutation] .
2. There may be associated vocal cord paresis.
3. Referred by a paediatric or adult neurologist /neuromuscular specialist, or clinical geneticist



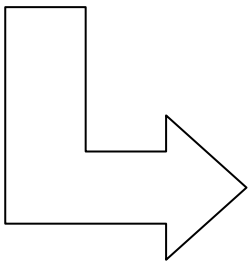
WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?

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 Rare Peripheral Neuropathy genes to be devised for each case by expertise from the testing organisation.
Please see accompanying documentation (Reilly M. *Practical Neurology* 2007;7;93-105)



HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

30-40

UKGTN Testing criteria

Patient name:

Patient postcode:

Name of referrer:

Title/Position:

Name of Disease/test:
Charcot Marie Tooth Disease, Axonal, type 2A2 / GANGLIOSIDE-INDUCEDDIFFERENTIATION-ASSOCIATED PROTEIN 1 (GDAP1)

Referrals will only be accepted from one of the following:

Referrer	Tick if this refers to you.
Clinical Geneticists and Specialist Neurologists after review with clinical expertise from list below.	
ION	
HAMMERSMITH	
BRISTOL	

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

Criteria	Tick if this patient meets criteria
Axonal or intermediate demyelinating peripheral neuropathy, (+/- associated vocal cord paresis). **AND**	
Isolated case or pedigree suggestive of autosomal dominant, or autosomal recessive inheritance **AND**	
Exclusion of common forms of CMT2/CMT1 (MPZ, GJB1, MFN2, and /or PMP22 del/dup, PMP22 mutation)	