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

TEST – DISORDER/CONDITION – POPULATION TRIAD			
Submitting laboratory:	**Newcastle Mitochondrial Laboratory London Institute of Neurology Oxford RGC**	**Approved:**	**Sept 2013**

1. Disorder/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	Mitochondrial DNA depletion syndrome (13 Gene Panel) See Appendix 1
2. OMIM number for disorder/condition	See Appendix 1
3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.	Presentations in childhood are with severe myopathies, hepatopathies and encephalopathies, which may have associated multi-system disease. The prognosis for normal independent life is very poor and death in childhood likely. Cardiomyopathy, movement disorders (often due to neuropathies), epilepsy, and dysphagia are common.
3b Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.	Some patients present simply with epilepsy. Seizures should be treated vigorously, as when poorly controlled, patients may progress from apparent good health to death in a matter on months.
4. Disorder/condition – mode of inheritance	Autosomal recessive
5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)	See Appendix 1
6a. OMIM number for gene(s) **6b HGNC number for gene(s)**	See Appendix 1 See Appendix 1
7a. Gene – description(s)	

Symbol	Description
C10orf2	MtDNA helicase (required for mtDNA replication); Twinkle
DGUOK	Deoxyguanosine kinase (localises to mitochondrial matrix)
MFN2	Mitofusin 2; a GTPase (localises to outer mitochondrial membrane, functions in mitochondrial fusion)
MPV17	MpV17 mitochondrial inner membrane protein (unknown function)
OPA1	Optic atrophy 1; a dynamin-related GTPase (localises to inner mitochondrial membrane, functions in mitochondrial fusion)
POLG	Catalytic subunit of the mtDNA polymerase
POLG2	Accessory subunit of the mtDNA polymerase
RRM2B	Small subunit of p53-inducible ribonucleotide reductase
SLC25A4	Skeletal muscle form of the adenine nucleotide translocator (localises to inner mitochondrial membrane)

	SUCLA2 — Beta subunit of the ADP-forming succinate-CoA ligase (localises to mitochondrial matrix) *SUCLG1* — Alpha subunit of the succinate-CoA ligase (localises to mitochondrial matrix) *TK2* — Thymidine kinase-2 (localises to mitochondrial matrix) *TYMP* — Thymidine phosphorylase
7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)	23.3 kbp
7c. GenU band that this test is assigned to for index case testing	GenU band H 2013/14
8. Mutational spectrum for which you test including details of known common mutations	Missense, nonsense, splice-site, small insertions/deletions. There are 3 to 5 autosomal recessive mutations in *POLG* which are common in populations of European origin (founder effect), and these will be excluded prior to proceeding to the panel test.
9a. Technical method(s)	1. Oxford - mutation screening of the coding regions and intron-exon boundaries of the genes listed using a next generation sequencing by synthesis approach: in solution targeted enrichment (HaloPlex) for the 13 genes followed by IIIumina MiSeq. Data analysis is undertaken using NextGENe software and an in house pipeline. All analysed bases are covered by a minimum of 30 reads. Sanger sequencing is undertaken to confirm variants and fill in gaps as necessary. 2. ION - mutation screening of the coding regions and intron-exon boundaries of the genes listed using a next generation sequencing by synthesis approach: Targeted enrichment of the 13 genes by the Illumina TruSeq Custom Amplicon (TSCA) method followed by analysis on an Illumina MiSeq. Demultiplexed fastQ files are generated using MiSeq Reporter software v2.0. Paired-end reads of each sample are aligned to the human genome, hg19, in NOVOALOGIN software. Read pileup and variant detection is performed in SAMTOOLS. Identified variants are annotated in ANNOVAR to generate a mutation report. Coverage of the targeted regions on a per sample basis is generated using in-house developed software called CovCheck and data is also analysed using NextGENe software and GenomeBrowse 1.1.1. All bases analysed are covered by a minimum of 100 reads with an average of 500. Sanger sequencing is used to confirm any pathogenic mutations detected and to fill in any gaps as necessary. 3. Newcastle - mutation screening of the coding regions and intron-exon boundaries of the genes listed

<table>
<tr><td></td><td>using a next generation sequencing by synthesis approach, based on in-solution targeted enrichment (HaloPlex) for the 13 genes followed by analysis on an Ion Torrent (Life Technologies). Data analysis is undertaken using NextGENe software and an in house pipeline. All analysed bases are covered by a minimum of 30 reads. Sanger sequencing is undertaken to confirm variants and fill in gaps as necessary.</td></tr>
<tr><td>9b If a panel test using NGS please state if it is a conventional panel or a targeted exome test.</td><td>Targeted gene panel test</td></tr>
<tr><td>9c. Panel/targeted exome Tests
i) Do the genes have 100% coverage? If not what is the strategy for dealing with the gaps in coverage?</td><td>Not all genes in the panel will have 100% coverage. Data obtained during validation has demonstrated the following average % coverage at ≥30 read depth:
<table><tr><th>Gene</th><th>%</th></tr><tr><td>C10orf2</td><td>100.0</td></tr><tr><td>DGUOK</td><td>100.0</td></tr><tr><td>MFN2</td><td>98.4</td></tr><tr><td>MPV17</td><td>100.0</td></tr><tr><td>OPA1</td><td>98.4</td></tr><tr><td>POLG</td><td>98.0</td></tr><tr><td>POLG2</td><td>87.5</td></tr><tr><td>RRM2B</td><td>98.6</td></tr><tr><td>SLC25A4</td><td>100.0</td></tr><tr><td>SUCLA2</td><td>81.3</td></tr><tr><td>SUCLG1</td><td>99.4</td></tr><tr><td>TK2</td><td>91.8</td></tr><tr><td>TYMP</td><td>84.9</td></tr><tr><td>TOTAL</td><td>96.1</td></tr></table>
Average read depth across the panel is approx. 500-750, and minimum acceptable read depth is 30 for HaloPlex (Oxford & Newcastle) and 100 for Illumina TSCA (ION).
The gaps will be filled in by Sanger sequencing as necessary to achieve 100% coverage for all genes.</td></tr>
<tr><td>ii) Does the test include MLPA?</td><td>No. MLPA for most genes will be available as an optional supplementary test. N.B. Exonic / whole gene deletions appear to be very rare for these genes. Although copy number analysis will not be included within the NGS pipeline in the first instance, this may be developed and added to the test in the future.</td></tr>
<tr><td>iii) Does this use sanger sequencing or Next Generation Sequencing (NGS)?</td><td>Primarily NGS, then Sanger sequencing to confirm variants and fill in gaps.</td></tr>
<tr><td>iv) If NGS is used, does the lab adhere to the Practice Guidelines for NGS?</td><td>Yes</td></tr>
<tr><td>10 Is the assay to be provided by the lab or is it to be outsourced to another provider? If to be outsourced, please provide the name of the laboratory.</td><td>Provided by the lab</td></tr>
</table>

11. Validation process

Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation

Validation is nearing completion at all 3 centres.

1. Validation has been undertaken for three HaloPlex assays (Inherited cardiomyopathies, Retinal/Joubert and Ataxia).

Results from cardiac validation (up to March 2013)

Total number of samples tested	35
Total number of known nucleotide variants	178
Total number of known unique variants tested	67
Sensitivity % of known unique variants detected (at 30x depth)	100%
Specificity False positive rate (variants not confirmed by Sanger sequencing)	4%

NextGENe® software is being used for data analysis. Analysis settings have been evaluated in liaison with Bioinformatics colleagues at the WTCHG and the Oxford Biomedical Research Centre.

Validation of this approach for the 13 genes in this panel is ongoing; coverage data has been obtained from 8 anonymised samples (contributing to the data summarised in 9c(i)), and analysis of 8 patients in whom variants have previously been identified by Sanger sequencing is ongoing.

2. To date 6 different Illumina TSCA panels (a total of over 1000 different amplicons) have been run and analysed in the ION laboratory on a research basis for 96 samples each. Over 300 blinded samples with 373 known variants detected by Sanger sequencing were analysed on these panels and all variants were detected. These included missense, nonsense, silent, splice mutations, flanking intronic variants and small indels up to 20bp in length. Also 33 pathogenic mutations detected in samples on the panels not previously analysed were all subsequently confirmed to be true using Sanger sequencing. The data from these 6 panels demonstrate that all previously known pathogenic mutations and polymorphisms can be detected using custom amplicon next generation sequencing panels. Although we haven't analysed this panel of genes to date, we expect that using the same quality parameters as previous panels that if a mutation is present in a gene it will be detected.

3. Validation of the NGS approach described in section 9a for the 13 genes in this panel is ongoing in the Newcastle laboratory, and will include analysis of at least 10 patients in whom variants have previously been identified by Sanger sequencing, for concordance.

As part of the final validation process, 10 samples that have previously been tested by Sanger sequencing of all 13 genes will be analysed by all 3 laboratories. The

	results will be compared in detail (including comparison of all variants detected) to confirm concordance across all 3 labs and with the previous Sanger sequencing. All three labs use the following variant filtering method. Variants detected are filtered using in house software to exclude point mutations at >1% allele frequency on NHLBI exome variant server (variants in EVS must also have data from at least 1000 chromosomes) and to check against a manually curated in house list of polymorphisms. The remaining variants are confirmed by Sanger sequencing and then investigated manually using Alamut as a basis for further evaluation of pathogenicity
12a. Are you providing this test already?	☒ **No** ☐ **Yes** However, the Oxford and Newcastle labs currently provide a service for 10 of these 13 genes by Sanger sequencing. *POLG* and *C10orf2* (*PEO1*) are already listed on UKGTN.
12b. If yes, how many reports have you produced? **Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.**	1. Approx. 400 for *POLG* sequencing in patients with suspected mitochondrial DNA depletion syndrome (from 2006-present, in full diagnostic setting), less for other genes 2. N/A 3. Approximately 250 reports (2006-present) for a range of mtDNA maintenance genes implicated in mtDNA depletion syndromes
12c. Number of reports mutation positive	1. 36 2. N/A 3. 15
12d. Number of reports mutation negative	1. 364 patients (multiple reports per patient in many cases, as genes have been tested separately or in groups of 2 or 3) 2. N/A 3. 235
13. For how long have you been providing this service?	1. We have provided a service for *POLG* & *C10orf2* since 2003 (initially by WAVE-DHPLC, and then by Sanger sequencing from 2006), and have added additional genes to the service from 2007 onwards. 2. N/A 3. 2006-present for *POLG*, *C10orf2* and *SLC25A4*; other mtDNA maintenance genes (*POLG2*, *TK2, DGUOK*, *MPV17, SUCLA2, SUCLG1, RRM2B*) added from 2008 onwards
14a. Is there specialised local clinical/research expertise for this disorder?	☐ **No** ☒ **Yes**

14b. If yes, please provide details	1. Professor Joanna Poulton, Professor and Honorary Consultant in Mitochondrial Genetics, Nuffield Dept Obstetrics and Gynaecology, The Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU 2. Professor Michael Hanna and Dr Shamima Rahman have research groups investigating mitochondrial disease both genetically and functionally. Professor Hanna and Dr Shamima Rahman run a HSS funded Mitochondrial Disease clinic at the National Hospital for Neurology and Neurosurgery. 3. Professor Doug Turnbull (adults) and Dr Robert McFarland (children) provide the NSCT/HSS Clinical Service in Newcastle and together with Professor Taylor run an active clinical and basic research programme as part of the Wellcome Trust Centre for Mitochondrial Research at Newcastle University.
15. Are you testing for other genes/disorders/conditions closely allied to this one? Please give details	Yes. All 3 centres test for a range of mitochondrial respiratory chain disorders within our remit as HSS funded centres for rare mitochondrial disorders. In particular, this service includes analysis for 5 common *POLG* gene mutations as a rapid initial test, and analysis of muscle & liver DNA for mtDNA depletion.
16. Based on experience what will be the national (UK wide) activity, per annum, for:	Based on current referral rates to the 3 HSS funded centres for rare mitochondrial disorders.
16a. Index cases	Approx. 150
16b. Family members where mutation is known	Approx. 50 (these will be tested by Sanger sequencing of the appropriate region)
17a. Does the laboratory have capacity to provide the expected national activity?	Yes. The 3 HSS Mitochondrial Rare Disease funded services in London, Oxford and Newcastle together have the capacity to provide the expected national activity.
17b. If your laboratory does not have capacity 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".	N/A
18. Please justify the requirement for another laboratory to provide this test e.g. insufficient national capacity.	N/A

EPIDEMIOLOGY

19a. Estimated prevalence of condition in the general UK population	Based on an incidence of 1 in 22,000 as determined below, and given an approx. UK annual birth rate of 800,000, one can perhaps expect approx. 36 cases to present each year. An accurate prevalence cannot be calculated.
19b. Estimated incidence of condition in the general UK population Please identify the information on which this is based	Based on: • Carrier frequency of autosomal recessive *POLG* mutation c.1399G>A (p.Ala467Thr) in populations of European origin is approx. 0.28% (NHLBI Exome Sequencing Project data) • *POLG* c.1399G>A (p.Ala467Thr) accounts for approx. 30% of autosomal recessive *POLG* mutations in our patient cohort • Approx. 50% of autosomal recessive *POLG*-related disease presents as mitochondrial DNA depletion syndrome (local data) • Autosomal recessive *POLG* mutations account for approx. 28% of mitochondrial DNA depletion syndrome (Spinazzola *et al*., 2009, *J. Inherit. Metab. Dis.*, **32** (2), 143-158) The incidence of mitochondrial DNA depletion syndrome can be estimated to be approx. 1 in 22,000.
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Using the above data, the carrier frequency of mitochondrial DNA depletion syndrome is estimated to be approx. 1 in 75 (1.3%).
21. Estimated penetrance Please identify the information on which this is based	To date there are no reports of non-penetrance to our knowledge, and therefore penetrance is likely to be very high.
22. Estimated prevalence of condition in the population of people that meet the Testing Criteria.	Approx. 12%

INTENDED USE

23. Please tick either yes or no for each clinical purpose listed.

Panel Tests: a panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

Diagnosis	☒ **Yes**	☐ **No**
Treatment	☒ **Yes**	☐ **No**
Prognosis & management	☒ **Yes**	☐ **No**
Presymptomatic testing (n/a for panel tests)	☐ **Yes**	☐ **No**
Carrier testing for family members (n/a for panel tests)	☐ **Yes**	☐ **No**
Prenatal testing (n/a for panel tests)	☐ **Yes**	☐ **No**

TEST CHARACTERISTICS

24. 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.

The analytical sensitivity for both the HaloPlex methodology (Oxford & Newcastle) and the Illumina TSCA methodology (ION) has been determined to be ≥95% (95% CI). A summary of the validation data on which this is based is given in section 11. Further validation is in progress to increase the number of unique variants tested and hence further refine the analytical sensitivity for these methodologies.

The analytical specificity of these NGS methodologies followed by Sanger sequencing to confirm/exclude variants is close to 100%.

25. Clinical sensitivity and specificity of test in target population

The *clinical sensitivity* of a test is the probability of a positive test result when condition is known to be present; the *clinical specificity* is the probability of a negative test result when disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity).

The clinical sensitivity is estimated to be approx. 80%, based on local data and Spinazzola *et al*., 2009, *J. Inherit. Metab. Dis.*, **32** (2), 143-158 (with the majority of the remaining cases likely due to mutation in as yet unidentified genes).

Clinical specificity is close to 100%, although variants of uncertain significance may be detected in a proportion of cases, preventing a definitive “negative” test result.

26. 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 condition or predisposition. It is measured by its *positive predictive value* (the probability of getting the condition given a positive test) and *negative predictive value* (the probability of not getting the condition given a negative test).

The positive predictive value is believed to be very high. There are no reported cases of non-penetrance to date.

The negative predictive value in the target population is estimated to be approx. 97%, based on 12% of target population having the condition and 80% clinical sensitivity.

For family tests (e.g. newborn siblings of affected patients), the negative predictive value is close to 100%.

27. Testing pathway for tests where more than one gene is to be tested

Please include your testing strategy if more than one gene will be tested and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram. This will be added to the published Testing Criteria.

N/A as all genes will be tested simultaneously in the panel. However, we have included results of relevant molecular genetic investigations within the testing criteria, and we also provide these tests within the laboratory.

CLINICAL UTILITY

28. How will the test change the management of the patient and/or alter clinical outcome?

Availability of this test will speed up diagnosis of patients with mutations in one of these genes, and also increase the proportion of cases in which a diagnosis is confirmed (since currently not all these genes will be tested in all cases of suspected mtDNA depletion syndrome). The diagnosis of mtDNA depletion syndrome cannot be unequivocally determined without identification of causative gene mutations.

Prognoses and management may depend on the causative gene and even on the specific mutation(s) identified; for example, in patients with liver failure, mitochondrial disease is usually a contraindication for liver transplant, but may still be appropriate in some cases of MDS due to *MPV17* mutation.

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29. Benefits of the test for the patient & other family members

Please provide a summary of the overall benefits of this test.

Finding causative mutation(s) in an affected child removes the need for further molecular or biochemical investigations, and can have an impact on prognosis and management.

Molecular genetic diagnosis also facilitates appropriate genetic counselling, and enables prenatal diagnosis or preimplantation genetic diagnosis where appropriate.

30. What will be the consequences for patients and family members if this test is not approved?

If the test is not approved, then the diagnosis will not be confirmed in some cases and will take longer in others. As discussed in questions 28 and 29, this may have consequences for prognosis and management, and also for anxiety, genetic counselling, prenatal diagnosis & preimplantation genetic diagnosis in family members.

31. 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.

No.

32. Please describe any specific ethical, legal or social issues with this particular test.

Variants of uncertain significance will be identified in less than 10% of cases (based on current experience of analysis of 10 of the 13 genes by Sanger sequencing). In rare cases (combined carrier frequency of mtDNA maintenance disorders ~2%), patients may be found incidentally to be a carrier of a mutation in another gene associated with a mitochondrial DNA maintenance disorder. Clinicians with specialist expertise in mitochondrial disease and mitochondrial genetics discuss these findings with the patients/families, as part of the HSS funded service for rare mitochondrial disorders.

33. Only complete this question if there is previously approved Testing Criteria and you do not agree with it.

Please provide revised Testing Criteria on the Testing Criteria form and explain here the changes and the reasons for the changes.

N/A

34. List the diagnostic tests/procedures that an index case no longer needs if this genetic test is available.

	Type of test	Cost (£)
Costs and type of imaging procedures		
Costs and types of laboratory pathology tests (other than molecular/cyto genetic test proposed in this gene dossier)	*POLG* & *C10orf2* sequencing. *DGUOK*, *MPV17*, *RRM2B*, *SUCLA2*, *SUCLG1* & *TK2* sequencing.	£600 £900
Costs and types of physiological tests (e.g. ECG)		
Cost and types of other investigations/procedures (e.g. biopsy)		
Total cost tests/procedures no longer required		**£1500**

This test would replace the existing genetic tests listed above.

Note that in some cases, other costs such as consultant time and costs of patient management will also be reduced.

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35. Based on the expected annual activity of index cases (Q15a), please calculate the estimated annual savings/investments based on information provided in Q33.

Number of index cases expected annually	150
Cost to provide tests for index cases if the genetic test in this gene dossier was not available (see Q34)	£1500
Total annual costs pre genetic test	£225,000
Total annual costs to provide genetic test	150 x £1020 = £153,000
Total savings	£72,000

36. REAL LIFE CASE STUDY

In collaboration with the clinical lead, describe TWO real case examples:

1. **prior to availability of genetic test**
2. **post availability of genetic test**

to illustrate how the test improves patient experience and the costs involved.

Case example one – pre genetic test

This female infant was born to consanguineous Asian parents. She had hypotonia from birth (May 2011). At 6 months of age (Nov 2011), she had profoundly delayed motor skills but normal intellect. On examination she was hypotonic, with head lag and weakness, and CK was elevated at 2000. Because of feeding difficulties with respiratory infections and poor weight gain, she was given nutritional support, initially nasogastric feeding. At this time, the paediatrician suspected a diagnosis of congenital muscular dystrophy or congenital myopathy, and so muscle biopsy was carried out and she was referred to paediatric neurology. Muscle histology showed ragged red fibres and COX negative fibres, highly suggestive of a diagnosis of mitochondrial myopathy. Blood DNA was tested for common mtDNA mutations and common POLG mutations, and results were normal. A muscle sample was then sent for mtDNA depletion analysis, which showed evidence of mtDNA depletion (reported Dec 2011), indicating a diagnosis of mtDNA depletion syndrome. The patient sadly died in late Dec 2011.

Nuclear genes associated with mtDNA depletion syndrome were sequenced in a stepwise manner, in accordance with available testing at the time: *POLG* & *C10orf2* analysis was reported normal in mid Jan 2012; *DGUOK*, *MPV17* & *RRM2B* analysis was reported normal in late Jan 2012; this was followed by *TK2* analysis, reported March 2012, which identified a homozygous pathogenic mutation. The identification of pathogenic *TK2* mutations confirmed the diagnosis, inheritance pattern, and opened up future reproductive choices for the family. The parents are now planning preimplantation genetic diagnosis.

PRE GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures	-	-
Costs and type of laboratory pathology tests	Plasma/blood biochem Muscle histology Initial genetic tests on blood DNA (mtDNA mutations, common *POLG* analysis) Genetic testing of muscle DNA (mtDNA depletion analysis) Further genetic testing of blood DNA (POLG, C10orf2, DGUOK, MPV17, RRM2B, TK2 stepwise)	£200 £300 £440 £170 £1710
Costs and type of physiological tests (e.g. ECG)	-	-
Cost and type of other investigations/procedures (e.g. biopsy)	Muscle biopsy	£650
Cost outpatient consultations (genetics and non genetics)		£1500
Total cost pre genetic test		**£4970**

Case example two – post genetic test

Referring case example one above, the benefits of the new panel test can be inferred. The new panel test would have enabled diagnosis approx. 2 months earlier, which would have been of enormous emotional benefit to the parents, so soon after the loss of their child. This would also have made it possible for the family to move forward more quickly with plans for further children.

POST GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures	-	-
Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	Plasma/blood biochem Muscle histology Initial genetic tests on blood DNA (mtDNA mutations, common *POLG* analysis) Genetic testing of muscle DNA (mtDNA depletion analysis)	£200 £300 £440 £170
Cost of genetic test proposing in this gene dossier		£1020
Costs and type of physiological tests (e.g. ECG)	-	-
Cost and type of other investigations/procedures (e.g. biopsy)	Muscle biopsy	£650
Cost outpatient consultations (genetics and non genetics)		£1500
Total cost post genetic test		**£4280**

37. Estimated savings between two case examples described £690

UKGTN Testing Criteria

Test name: **Mitochondrial DNA Depletion 13 Gene Panel**	
Approved name and symbol of disorder/condition(s): Mitochondrial DNA depletion syndrome (13 Gene Panel) See Appendix 1	**OMIM number(s):** See Appendix 1
Approved name and symbol of gene(s): See Appendix 1	**OMIM number(s):** See Appendix 1

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 Paediatric Hepatologist	
Consultant Intensive Care Paediatrician	
Consultant Metabolic Paediatrician	
Consultant Paediatric Neurologist	
Consultant Clinical Geneticist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Reduced mtDNA copy number in liver or muscle, or mosaic mtDNA depletion in fibroblasts	
And 3-5 common *POLG* mutations excluded for patients of European origin	
OR Infantile onset acute liver failure	
And raised lactate	
And liver biopsy not possible	
And 3-5 common *POLG* mutations excluded for patients of European origin	
OR Strong clinical suspicion of mitochondrial DNA depletion syndrome but biopsy of appropriate tissue (e.g. liver and/or muscle) not possible, for example if patient is deceased or family will not consent to biopsy	
And 3-5 common *POLG* mutations excluded for patients of European origin	

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Additional Information:
For panel tests: At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known 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.

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Appendix 1

Disorders and associated genes in panel test

OMIM standard name of condition	OMIM symbol	OMIM number	HGNC symbol	HGNC number	OMIM number for gene	No. families reported
Mitochondrial DNA depletion syndrome 1 (MNGIE type)	MTDPS1	#603041	*TYMP*	3148	*131222	>40 (OMIM)
Mitochondrial DNA depletion syndrome 2 (myopathic type)	MTDPS2	#609560	*TK2*	11831	*188250	>12 (OMIM)
Mitochondrial DNA depletion syndrome 3 (hepatocerebral type)	MTDPS3	#251880	*DGUOK*	2858	*601465	>10 (OMIM)
Mitochondrial DNA depletion syndrome 4A (Alpers type)	MTDPS4A	#203700	*POLG*	9179	*174763	>50 (OMIM)
Mitochondrial DNA depletion syndrome 4B (MNGIE type)	MTDPS4B	#613662	*POLG*	9179	*174763	4 (OMIM)
Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with methylmalonic aciduria)	MTDPS5	#612073	*SUCLA2*	11448	*603921	19 (OMIM)
Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	MTDPS6	#256810	*MPV17*	7224	*137960	>7 (OMIM)
Mitochondrial DNA depletion syndrome 7 (hepatocerebral type)	MTDPS7	#271245	*C10orf2*	1160	*606075	>20 (OMIM)
Mitochondrial DNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy)	MTDPS8A	#612075	*RRM2B*	17296	*604712	5 (OMIM)
Mitochondrial DNA depletion syndrome 8B (MNGIE type)	MTDPS8B	#612075	*RRM2B*	17296	*604712	1 (OMIM)
Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	MTDPS9	#245400	*SUCLG1*	11449	*611224	4 (OMIM)
Genes in the panel that are not associated with mtDNA depletion syndrome to date, but are associated with other disorders of mtDNA maintenance (see dossier #139), and hence have the potential to cause mtDNA depletion syndrome			*POLG2*	9180	*604983	0
			SLC25A4	10990	*103220	0
			OPA1	8140	*605290	0
			MFN2	16877	*608507	MtDNA depletion was detected in 3 CMT2A patients (Vielhaber et al. 2013)