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

Submitting laboratory: Leeds RGC

1. Disorder/condition – approved name (please provide UK spelling if different from US) and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website).
If NGS panel test, please provide a name.
If this submission is for a panel test please complete the Excel spread sheet, Appendix 1, available for download from the UKGTN website, and list all of the conditions grouped by sub panels if applicable.

White Matter Disorders (Leukodystrophy & Leukoencephalopathy) 96 gene panel

2. OMIM number for disorder/condition
If a panel test – see 1 above. If a number of subpanels exist with different clinical entry points e.g. cancer panel test but different subpanels for different types of cancer (breast cancer, colon, phaeochromocytoma), then please list the sub panels here – providing name of each sub panel.

1) Leukodystrophy & Mitochondrial Leukoencephalopathy 96 gene panel (all genes)
2) Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease 12 gene panel
3) Peroxisome Disorders 16 gene panel
4) Mitochondrial Leukoencephalopathy 33 gene panel
5) Leukoencephalopathy with Vanishing White Matter 5 gene panel
6) X-linked Adrenoleukodystrophy 1 gene panel
7) Cockayne Syndrome 2 gene panel
8) Aicardi-Goutieres Syndrome 7 gene panel

3a. Disorder/condition – to help commissioners to understand the impact of this condition please provide, in laymen's terms (e.g tubes in the kidney (renal tubule) or low sugar in the blood (hypoglycaemia)), a brief (2-5 sentences/no more than 50 words) description of how the disorder(s) affect individuals and prognosis.

Leukodystrophies are disorders of the white matter of the brain, usually present at birth and most also involve progressive ongoing neurodegeneration. They are typically associated with learning difficulties and a wide range of development and other clinical problems, which often worsen relentlessly over time and may cause early death.

3b. Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.

Leukodystrophy refers to a white-matter abnormality with a known genetic cause, causing dysfunctional development of the myelin sheath in neurons of the central nervous system, visible on neuroimaging. In general, these disorders are progressive and result in intellectual disability and a range of other neurological presentations, but in many cases can be part of a syndrome with additional systemic features some of which can be very severe. Leukoencephalopathy is a more general term referring to white-matter abnormalities which may have acquired, rather than genetic, aetiology, and which may not specifically be caused by problems in myelin development.

4. Disorder/condition – mode of inheritance
If this submission is for a panel test, please complete the mode of inheritance for each condition in the table in appendix 1.

N/A

5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)
If this submission is for a panel test please complete the Excel spread sheet, Appendix 1, available for download from the UKGTN website, and list all of the genes grouped by sub panels if applicable.

N/A

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6a. OMIM number(s) for gene(s)
If a panel test – see 5. above

N/A

6b. HGNC number(s) for gene(s)
If a panel test – see 5. above

N/A

7a. Gene – description(s)
If this submission is for a panel test, please provide total number of genes and if there are subpanels, please also list the number genes per sub panel.

1) Leukodystrophy & Mitochondrial Leukoencephalopathy 96 gene panel (all genes)
2) Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher disease 12 gene panel
3) Peroxisome Disorders 16 gene panel
4) Mitochondrial Leukoencephalopathy 33 gene panel
5) Leukoencephalopathy with Vanishing White Matter 5 gene panel
6) X-linked Adrenoleukodystrophy 1 gene panel
7) Cockayne Syndrome 2 gene panel
8) Aicardi-Goutieres Syndrome 7 gene panel

7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)
(n/a for panel tests)

N/A

7c. GenU band that this test is assigned to for index case testing.
For NGS panel tests if there are sub panels, please provide GenU per subpanel.

1) Leukodystrophy & Mitochondrial Leukoencephalopathy 96 gene panel (all genes) - Band H
2) Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease 12 gene panel - Band G
3) Peroxisome Disorders 16 gene panel - Band G
4) Mitochondrial Leukoencephalopathy 33 gene panel - Band G
5) Leukoencephalopathy with Vanishing White Matter 5 gene panel - Band G
6) X-linked Adrenoleukodystrophy 1 gene panel - Band G
7) Cockayne Syndrome 2 gene panel - Band G
8) Aicardi-Goutieres Syndrome 7 gene panel – Band G

8. Mutational spectrum for which you test including details of known common mutations
(n/a for panel tests)

N/A

9a. Technical method(s) – please describe the test.

Genomic regions comprising the consensus coding regions of 6000+ disease genes are captured using the Agilent SureSelectXT Focused Exome. Libraries are prepared using standard reagents as per the manufacturer's protocol. Sequencing is performed on an Illumina Next-Generation Sequencing (NGS) platform, typically the HiSeq 2500 utilising the rapid run settings, multiplexing 6 samples per lane. Sufficient sequencing is performed to cover the >95% of the targeted by genes to a minimum of 15X read-depth, generally producing average exome and target coverage of approximately 100X.

An in-house bioinformatics pipeline is used to process the data. In summary, genomic alignment of raw Illumina data is performed using the Burrows-Wheeler Aligner (BWA-MEM; Li H. and Durbin R. (2010) Fast and accurate long-read alignment with Burrows-Wheeler Transform. Bioinformatics, Epub. [PMID: 20080505]), post-processing using Picard and the GATK-lite suite of applications (Broad Institute), variant calling using GATK-lite (Broad Institute), and variant annotation using Alamut Batch (Interactive Biosoftware).

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Appropriate genes for analysis are decided at a multidisciplinary meeting (MDT) comprising at least a clinical scientist, a consultant clinical geneticist, a consultant paediatric neurologist with special interest in white-matter disorders, and a neuroradiologist. Assessment of the provided clinical phenotypes and electronic copies of neuroimaging is essential. A differential diagnosis, comprising genes from one of the sub-panels is made. This will be incorporated into a highly targeted "first sweep" genetic analysis, to minimise the detection of incidental findings and variants of uncertain clinical significance. If clear causative variant(s) are not detected, a more general genetic analysis (which may comprise all 96 genes from the panel) is applied, if this is deemed clinically appropriate by the MDT. Where a specific diagnosis and/or request for a specific sub-panel has been made by an external referrer, this will be taken into account at the MDT, and the referrer will be notified if the decision of the MDT differs from their specified referral.

Assessment of the chosen genes takes place using Microsoft Visual Basic (VBA)-driven analysis templates, which filter the raw variant list and determine coverage of the targeted regions. Standard "moderate" filtering criteria involve the removal of any variants outside the selected gene list, any variants with a dbSNP minor allele frequency (rsMAF) exceeding 0.5%, any synonymous variants in coding regions, any variants in the 3' untranslated region, and any variants further than 10 nucleotides outside a coding exon; internal data indicates a sensitivity exceeding 98.5% for likely-pathogenic variation (n = 1,250 known pathogenic and likely-pathogenic variants detected historically by this laboratory). A "relaxed" filtering criteria is available for assessment, but not routinely used for reporting. Any variants passing the filtering stage are assessed manually, adhering to ACGS Best Practice. Coverage figures are reported at 15X and 30X read-depths, and may be assessed for specific single genes if deemed appropriate by the MDT. All clinically-significant variants are confirmed with Sanger sequencing.

Exonic dosage is calculated by comparative assessment of intra-lane read-depths; this method is not diagnostically validated, therefore negative results are not reported. Any clinically-relevant copy number imbalances are confirmed and reported using a second validated method.

9b. For panel tests, please specify the strategy for dealing with gaps in coverage.

Due to the size of the panels analysed, it is not feasible to address all coverage gaps. Validation data indicate >95% sensitivity for single nucleotide variants (SNVs) within the targeted regions of all sub-panels. Overall % coverage at 15X and 30X is stated on reports, and may be assessed for specific single genes if deemed appropriate by the MDT. Details (e.g. genomic coordinates) of specific gaps are available by request, in order to facilitate gap-filling.

For cases where X-linked adrenoleukodystrophy is within the differential diagnosis, exons 7-10 (which are not covered by the NGS analysis) are analysed separately by Sanger sequencing.

9c. Does the test include MLPA?
(For panel tests, please provide this information in appendix 1)

No. Exonic dosage is calculated from NGS data, however, this method is not diagnostically validated and negative results are not reported. Any clinically-relevant copy number imbalances are confirmed and reported using a second validated method. If detected in NGS data, PLP1 duplications will be validated by MLPA. The main issue with the NGS dosage data is specificity, rather than sensitivity (i.e. multiple single-exon findings outside our standard relative dosage "normal" range of 0.8-1.2 are detected in most patients; these are generally single, isolated events, which tend to be ignored, especially if coverage is low. The complete duplication or deletion of a whole gene or contiguous set of exons is typically extremely obvious and would always be followed-up, in this case likely by MLPA or aCGH). Additionally, the coverage of PLP1 during validation runs was found to be 100% at 30X; we have found dosage calling to be >95% sensitive in comparable panel tests at this level of coverage. Reports explicitly state that dosage abnormalities are not excluded; users are free to also order PLP1 MLPA if a diagnosis of Pelizaeus-Merzbacher disease is strongly suspected, however, we are very confident that all such cases will be detected and validated through our pipeline.

9d. If NGS is used, does the lab adhere to the Association of Clinical Genetic Science Best Practice Guidelines for NGS?

Yes.

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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 and a copy of their ISO certificate or their CPA number.

Assay is provided by the lab.

11. Validation process

Please explain how this test has been validated for use in your laboratory, including calculations of the sensitivity and specificity for the types of mutations reported to cause the clinical phenotype. Note that the preferred threshold for validation and verification is ≥95% sensitivity (with 95% Confidence Intervals). Your internal validation documentation can be submitted as an appendix (and will be included in the published Gene Dossier available on the website). The validation information should include data on establishing minimum read depth and horizontal coverage for the regions of interest, reproducibility of the pipeline, accuracy of variant calling, filtering of common variants and artefacts.
If this submission is for a panel test, please provide a summary of evidence of instrument and pipeline validation and complete the tables below.

Instrument (HiSeq2000) and bioinformatics pipeline was validated on equivalent panel chemistry (hereditary cancer genes panel), enabling a comparison to be made against sensitivity of existing pipelines (Sanger sequence analysis and NGS analysis based on enrichment by long range PCR). 100% concordance was recorded for 480 variants (101 unique) between the panel test and gold-standard PCR-based analysis.

Specific validation of the reagent used for this panel (Agilent SureSelectXT Focused Exome) involved a variant detection assessment (unfiltered) against an established reagent ("SelGen" selected genes NGS reagent analysis), an assessment of the variant filtering criteria used, and an assessment of the sensitivity of the specific panel(s) used in this service as a function of read-depth, based on internal and published NGS data.

Variant detection sensitivity of reagent:

A panel of 590 known unique genomic variants from a panel of 125 diagnostically relevant genes ("SelGen") across 4 validation samples (two male, two female) was assayed on the Focused Exome reagent, using the standard laboratory protocol and bioinformatics pipeline. No additional filtering was applied. 561 were detected.

Of the 29 discordant variants, 24 were in genes which have no/low coverage on the exome reagent. These genes were not part of this diagnostic panel, and would be omitted from any putative diagnostic panel on the basis of low coverage during our laboratory's defined validation/feasibility studies; they were therefore outside the scope of the assay. Of the remaining 5 variants (out of a total of 555) in valid genes, 4 were found in isolated regions of zero NGS coverage. The remaining variant was a call with a very low vcf quality score and a skewed allele balance (17 of 89 reads) in a gene with a known pseudogene (HYDIN NM_001270974.1:c.3840G>A); this was deemed likely to be a pseudogene-derived artefact, although this was not formally proven as the measured sensitivity was already >98%.

550 of 555 variants within valid genes were therefore detected by the clinical exome technical process, a measured sensitivity of 99%, minimum sensitivity of 98% at 95% confidence. The only undetected variants were in low coverage and/or pseudogenic regions; sensitivity is therefore a function of coverage (mostly) and uniqueness of target sequence.

For panel tests:

Sensitivity 98% (95% CI)

Read depth minimum cut off:15X

	Previously tested	NGS test concordant results	NGS False negative
Number of patient samples	**4**	**-**	**-**
Unique variants (total)	**555**	**550**	**5**
SNV	**536**	**531**	**5**
Indel (1bp to 18 bp)	**19**	**19**	**0**
CNV	**0**	**0**	**0**

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Panel-specific sensitivity figures

A set of known variants within the targeted genes is not available, due to a paucity of positive controls and the expense of sequencing large numbers of samples using this technical pipeline. The sensitivity figures at two measured read-depths (15X and 30X), derived from local data and published data using a comparable informatics pipeline (Meynert et al, BMC Bioinformatics. 2013 Jun 18;14:195), were used to estimate a minimum sensitivity for each representative sub-panel.

Meynert et al. 2013 (supplementary data) derived a single-nucleotide variant (SNV) sensitivity figure (lower 95% confidence interval) of 98.8% at 30X and 96.2% at 15X for exome-based testing (largely agnostic of reagent and platform, using a consistent bioinformatics pipeline comparable to ours).

Local data using the Focused Exome reagent and our standard pipeline supports these figures:

38 of 38 variants with coverage between 15X and 30X were detected (100% sensitivity; 93.6% minimum sensitivity at 95% CI).

472 of 473 variants with coverage >30X were detected (99.8% sensitivity, 99% minimum sensitivity at 95% CI).

Local data were not subject to a downsampling analysis due to the potential for introducing bias when imposing such methods using public domain tools (personal observation).

The SNV sensitivity of the entire set of 96 leukodystrophy genes, and of the representative sub-panels, was assessed (using the 15X and 30X thresholds, and the Meynert 2013 sensitivity figures, which use a larger sample-size than was possible in our hands).

It is assumed that these figures represent an under-estimate of SNV sensitivity, as they make the assumption that all nucleotides with fewer than 15 reads have zero sensitivity; in our hands, 17 of 45 (38%) of variants <15X were detected in a validation experiment, and the vast majority of false-negatives (27 of 28) were in regions with 0X or 1X coverage. Sensitivity estimates are also based on heterozygous SNPs, and would be higher for homozygotes (Meynert et al. estimate a minimum read-depth of 3X is required to detect homozygous variants at 95% sensitivity in typical genomic assays).

Sub-Panel:	# Genes:	15X coverage:	30X coverage:	Estimated SNV sensitivity:	Notes:
Leukodystrophy & Mitochondrial Leukoencephalopathy (whole panel)	96	97.57%	93.76%	**96.30%**	Excluding ABCD1 exons 7-10; can be analysed separately if phenotypically relevant.
Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease	12	96.19%	89.59%	**94.86%**	Most commonly-mutated genes in literature are PLP1 (Pelizaeus-Merzbacher disease; 100% coverage at 30X, SNV sensitivity >98%) and GJC2 (Hypomyelinating leukodystrophy 2; 98.8% coverage at 15X, SNV sensitivity >97%).
Peroxisome Disorders	16	99.77%	96.96%	**98.50%**	Excluding ABCD1 exons 7-10; can be analysed separately if phenotypically relevant.
Mitochondrial Leukoencephalopathy	33	97.54%	94.36%	**96.28%**	
Leukoencephalopathy with Vanishing White Matter	5	99.32%	96.05%	**98.04%**	
X-linked Adrenoleukodystrophy	1	100.00%	100.00%	**98.80%**	ABCD1 exons 1-6 covered by NGS, exons 7-10 covered by Sanger sequencing.
Cockayne Syndrome	2	100.00%	97.82%	**98.74%**	
Aicardi-Goutieres Syndrome	7	99.83%	96.83%	**98.56%**	

The sensitivity figures, however, likely over-estimate the ability of the analysis to detect copy number variants, particularly those of an intermediate size (30bp - 1 exon). Local validation (see above) detected 19 of 19 known indels between 1 and 18bp in size (100% measured sensitivity; 87.1% minimum sensitivity 95% CI), however, local experience with our NGS pipeline also indicates an upper detection limit of around 50-60bp in size for deletions at very high read-depth, and this figure is likely to be lower at the ~100X average coverage across this panel. This is an acknowledged limitation of NGS-based

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assays in general; the specific implications for the mutation spectrum addressed by this panel are untested.

Specificity at least 92.3% (95% CI)

(Calculated using 'Jeffreys Interval')

	Variant confirmed by other method	NGS False positive
29 patient samples with a variant detected by NGS		
Unique variants (total)	**31**	**0**
SNV	**23**	**0**
Indel (1bp to 25 bp)	**7**	**0**
CNV	**1**	**0**

Variant filtering validation:

Variant filtering is applied as a standard part of the analysis. The standard criteria ("moderate") are as follows:

- By gene
- By location (within coding region +/-10bp)
- By minor allele frequency (dbSNP minor allele frequency (rsMAF) <0.5%)
- By coding consequence (synonymous coding variation excluded)

Internal validation (comparing those criteria to 1249 unique "likely pathogenic" (class 4) and "pathogenic" (class 5) variants derived from the laboratory's service history) indicated a measured sensitivity of 98.9% (1235/1249 detected, 98.2% sensitivity 95% CI); of the 14 "missed" variants, 4 were relatively high-frequency variants in very common recessive conditions, 5 were synonymous exonic variants with a proven effect on splicing, and 5 were variants beyond the +/-10bp region with a proven effect on splicing. None of the genes included on this panel underlie common recessive conditions with any known mutations exceeding 0.5% rsMAF (therefore making the first criteria irrelevant). We believe that, for the majority of the genes on this panel, there is little published evidence of characterisation of non-coding splicing variants outside of the consensus donor/acceptor dinucleotides, and therefore the impact of the second two criteria is likely to be minimal.

In addition, a "relaxed" filtering criteria is available (this is not reported as standard, but may be informally applied by analysts when the "moderate" criteria return no variants of clinical significance, or a single heterozygous variant in a recessive gene) which will include synonymous variation and common recessive mutations (up to 2% rsMAF), at the expense of specificity.

All variants which pass the filtering criteria are assessed manually by an analyst.

12a. Are you providing this test already?

Yes

12b. If yes, how many reports have you produced?

Sanger Based Tests	NGS Based Tests
	3

12c. Number of reports with a pathogenic (or likely pathogenic) mutation identified?

Sanger Based Tests	NGS Based Tests
	1

12d. Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.

First report issues November 2015; all reports produced in a diagnostic setting.

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13a. Is there specialised local clinical/research expertise for this disorder?
Yes
13b. If yes, please provide details
Dr JH Livingston Consultant Paediatric Neurologist (Leeds Teaching Hospitals NHS Trust) and Honorary Clinical Associate Professor (University of Leeds) is the national lead for the Inherited White Matter Interest Group of the British Paediatric Neurology Association and is the lead for the proposal to NHS England to agree national commissioning for an Inherited White Matter Disorders service. He has a research interest in leukodystrophies, particularly white matter disorders associated with intracranial calcification and is the co-lead of the leukodystrophy GECIP for the 100K genome project. **Prof EG Sheridan** Consultant Clinical Geneticist (Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust), Professor of Clinical Genetics (Medical Genetics Research Group, University of Leeds) has both a clinical and research interest in genetic disorders of white matter, focussing particular on rare recessive causes prevalent in sub-populations within Yorkshire which practice consanguineous marriage.
14. If using this form as an Additional Provider application, please explain why you wish to provide this test as it is already available from another provider.
N/A

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EPIDEMIOLOGY

15. Estimated prevalence and/or incidence of conditions in the general UK population

For panel tests, please provide estimates for the conditions grouped by phenotypes being tested.

Prevalence is total number of persons with the condition(s) in a defined population at a specific time (i.e. new and existing cases).

e.g. CF prevalence approx. 12 per 100,000 with UK population of approx. 63 million the prevalence of affected individuals in the UK is 7560

Incidence is total number of newly identified cases in a year in a defined population. e.g. CF incidence 1/2650 live births in a UK population with 724,000 live births in a year = 273 new cases a year

Please identify the information on which this is based.

Due to the challenges in diagnosing white matter disorders, the prevalence of leukodystrophies and related conditions are unclear. Estimates vary widely, from between 1 in 50,000 [Germany; Heim et al. Am. J. Med. Genet. 71 (1997) 475–478] to 1 in 7,663 [USA; Bonkowsky et al. Neurology 75 (2010) 718–725].

Assuming the more recent, higher published prevalence figure (1 in 7,663) is accurate, population of 57 million in England and Wales in 2013 (Office for National Statistics), and a birth rate of 695,000 in England and Wales in 2014 (Office for National Statistics):

Total Prevalence (England and Wales): ~7,500

16. Estimated gene frequency (Carrier frequency or allele frequency)

Please identify the information on which this is based.

n/a for panel tests.

N/A

17. Estimated penetrance of the condition. Please identify the information on which this is based

n/a for panel tests

N/A

18. Estimated prevalence of conditions in the population of people that will be tested.

n/a for panel tests.

N/A

INTENDED USE (Please use the questions in Annex A to inform your answers)

19. 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**

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TEST CHARACTERISTICS

20. Analytical sensitivity and specificity

The *analytical sensitivity* of a test is the proportion of positive results correctly identified by the test (true positive/true positive + false negative). The *analytical specificity* of a test is the proportion of negative results correctly identified by the test (true negative/true negative + false positive).

This should be based on your own laboratory data for (a) the specific test being applied for or (b) the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up. Please specify any types of mutations reported to cause the clinical phenotype that cannot be detected by the test.

Note that the preferred threshold is ≥95% sensitivity (with 95% Confidence Intervals).

Analytical sensitivity (detection of SNVs) for the whole panel, plus representative sub-panels are summarised below, from validation data. Where this figure is below 95% (Hypomyelination sub-panel), this is anticipated to be an underestimate as the coverage of the most commonly-mutated genes (PLP1 & GJC2) indicates sensitivity >97%.

Sub-Panel:	# Genes:	15X coverage:	30X coverage:	Estimated SNV sensitivity:	Notes:
Leukodystrophy & Mitochondrial Leukoencephalopathy (whole panel)	96	97.57%	93.76%	**96.30%**	Excluding ABCD1 exons 7-10; can be analysed separately if phenotypically relevant.
Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease	12	96.19%	89.59%	**94.86%**	Most commonly-mutated genes in literature are PLP1 (Pelizaeus-Merzbacher disease; 100% coverage at 30X, SNV sensitivity >98%) and GJC2 (Hypomyelinating leukodystrophy 2; 98.8% coverage at 15X, SNV sensitivity >97%).
Peroxisome Disorders	16	99.77%	96.96%	**98.50%**	Excluding ABCD1 exons 7-10; can be analysed separately if phenotypically relevant.
Mitochondrial Leukoencephalopathy	33	97.54%	94.36%	**96.28%**	
Leukoencephalopathy with Vanishing White Matter	5	99.32%	96.05%	**98.04%**	
X-Linked Adrenoleukodystrophy	1	100.00%	100.00%	**98.80%**	ABCD1 exons 1-6 covered by NGS, exons 7-10 covered by Sanger sequencing.
Cockayne Syndrome	2	100.00%	97.82%	**98.74%**	
Aicardi-Goutieres Syndrome	7	99.83%	96.83%	**98.56%**	

Analytical specificity was measured at 100% (92.3% at lower 95% CI).

The methodology used will not detect pathogenic mutations greater than 10bp outside the coding regions of the genes analysed. It is also not validated to detect large copy number variants; although such variants can and have been identified, the sensitivity for their detection is unknown.

21. 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).

Please provide the best estimate. UKGTN will request actual data after one year service.

For a panel test, the expected percentage diagnostic yield for the test in the target population can be presented as an alternative to clinical sensitivity and specificity?

Will vary depending on diagnostic criteria applied.

This panel contains the majority of known leukodystrophy genes; the majority of genes outwith this service cause syndromic presentations with specific clinical features. Literature indicates [Parikh et al.

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Molecular Genetics and Metabolism 114 (2015) 501–515] around 50-70% of white matter disorders may achieve a positive diagnosis using all currently available diagnostic investigations (imaging, metabolics and genetics). On this basis, diagnostic yield is anticipated to approach 50%, although in practice the real figure may be lower, as many diagnoses with clear clinical phenotypes may be made using single-gene tests prior to considering this service.

Comparable services offered by this laboratory using this reagent and broad methodology have achieved a diagnostic yield of 46%.

22. 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).

Not currently requested for panel tests

N/A

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

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 for panel tests

N/A

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CLINICAL UTILITY

24. How will the test change the management of the patient and/or alter clinical outcome? Please summarise in 2-3 sentences – no more than 50 words.

For many patients with a leukodystrophy no final diagnosis is reached and a prolonged series of expensive and sometimes distressing investigations are performed. The new test would enable rapid diagnosis, appropriate genetic counselling and early treatment (where relevant eg Hematopoietic stem cell transplantation (HSCT) in XALD).

25. Please provide full description on likely impact on management of patient and describe associated benefits for family members. If there are any cost savings AFTER the diagnosis, please detail them here.

Rapid diagnosis of a leukodystrophy would have many benefits for the patients and family. These include:

- Immediate access to treatments where relevant. eg HSCT for pre-symptomatic X-ALD or MLD.
- Enabling screening for and prevention of associated co-morbidities.
- Appropriate prognostication enabling life planning and referral to relevant support services.
- Accessing relevant information about the disease and contact with other families affected.
- Appropriate genetic counselling to enable reproductive choice and advice to other family members at risk.

Cost savings post-diagnosis would include avoidance of further unnecessary and expensive investigations and referrals and, in many cases, avoidance of further hospital admissions.

26a. If this test was not available, what would be the consequences for patients and family members? Please describe in not more than 50 of words.

Lack of a diagnosis results in a prolonged “odyssey” of expensive and increasingly invasive tests and referrals. Repeated MRI scans may be required. Preventable co-morbidities could not be identified. Life planning is difficult for families with no diagnosis. In the absence of a diagnosis, accurate genetic advice and counselling cannot be given and pre or ante-natal diagnosis will not be possible.

26b. The consequences for patients and family members if this test was not available – if required please expand on the response provided in question 26a.

Delay in diagnosis or no diagnosis is distressing for families affected with a rare disease. A diagnosis enables the process of adjustment to the diagnosis to begin. For an increasing number of leukodystrophies therapeutic studies are available and a diagnosis will enable patients to access these. Treatment and management of relevant co-morbidities can be provided. Accurate genetic counselling facilitates informed reproductive choice.

27. 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.

For many of the conditions covered by this panel, a biochemical or metabolic test exists, however, no single test diagnoses all conditions covered. The main advantage of this molecular genetic approach is the ability to diagnose a very broad range of LDs in early life using one diagnostic strategy, potentially prior to developing additional features that clarify the phenotype in later childhood, and without requiring a battery of different tests and blood draws. In many cases, alternative diagnostic strategies involve further imaging techniques (MRI, PET scans) and/or invasive sampling (tissue biopsies) which can be extremely distressing for patients (who almost invariably have moderate-to-severe learning disability) and families.

28. Please list any genes where the main phenotype associated with that gene is unrelated to the phenotype being tested by the panel. For example, lung cancer susceptibility when testing for congenital cataract because ERCC6 gene (primarily associated with lung cancer) is included in a panel test for congenital cataract.

Several genes cause variable, syndromic presentations which may be associated with white matter

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abnormalities (e.g. ERRC6 and ERCC8 are associated with Cockayne syndrome, which does not invariably present with leukoencephalopathy), however, in all cases, these are paediatric-onset and frequently associated with brain abnormalities, and therefore unlikely to be identified as an incidental finding in patients referred with leukodystrophies identified on neuroimaging.

Dominant mutations in the SDHB gene have been associated with very high endocrine tumour risks (phaeochromocytoma, paraganglioma) and potentially with Cowden syndrome, disorders of a generally adult onset. Such mutations are exceptionally rare in the general population, and are therefore unlikely incidental findings in patients with negative family history. The mutation associated with leukodystrophy (p.Asp48Val; J Med Genet. 2012 Sep;49(9):569-77 & Mol Genet Metab Rep. 2015 Dec;5:51-54) has not been associated with these conditions.

29. If testing highlights a condition that is very different from that being tested for, please outline your strategy for dealing with this situation.

The detection of variants within the SDHB gene that predispose to cancer will be reported, as these potentially have a significant impact on the health of the patient and their family.

30. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out by your lab e.g. Noonan Spectrum Disorders 12 Gene Panel replaced multigene Sanger test for KRAS, RAF1, PTPN11 and SOS1? If so, please provide details below.

No.

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

There are no particular ethical/legal or social considerations associated with this test.

32. REAL LIFE CASE STUDY
Please provide a case study that illustrates the benefits of this test

A 13 month old girl was referred to paediatric neurology because of developmental delay. She had a history of stridor from the neonatal period to 6 months of age. She was noted to be slow in development from the outset with poor head control, inability to sit at 13 months and floppiness. From the age of 4 months she had developed rotatory nystagmus.

She had the following normal investigations: Urine organic, amino acids, MPS screen. Blood lactate, ammonia, CK, TSH, T4, acyl carnitine and white cell enzymes.

Array CGH was performed, identifying no clinical abnormality.

MRI at one year showed diffuse hypomyelination and follow up MRI at 18 months confirmed this.

Testing for Pelizaeus Merzbacher-like disorder was considered, however it was decided to perform the hypomyelination panel test; the majority of the genes associated with hypomyelinating conditions are not available elsewhere in the UK.

This identified a mutation in *TUBB4A*, c.785G>A p.(Arg262His). This is a missense change affecting the tubulin beta 4A protein, associated with neuronal development. The mutation affects a residue which has shown to be essential for structure and function in other beta tubulin analogs, and has been reported in the literature three times arising *de novo* in patients with hypomyelinating leukodystrophy. It was subsequently shown to be absent in the parents, confirming a *de novo* aetiology, and that the mutation was the cause of the patient's phenotype. The patient was given a genetic diagnosis of hypomyelinating leukodystrophy-6 (HLD6).

This result has enabled the following:

1. A specific diagnosis to be given to the parents.
2. Information about the disease and its prognosis.
3. Carrier testing and genetic counselling; the parents are now aware that the recurrence risk associated with this *de novo* condition is likely to be low, allowing them to plan for future pregnancies.
4. Avoidance of any other investigations, in particular, invasive and expensive ones such as lumbar puncture or muscle biopsy.

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5. Although there are currently no treatment trials underway for this disease, knowing the diagnosis will enable early participation in treatment studies if and when they are initiated.
6. Participation in other research studies about this disease will be possible.

TESTING CRITERIA

33. Are previously approved Testing Criteria available that define the clinical entry point for this test? No Testing Criteria are available: http://ukgtn.nhs.uk/find-a-test/testing-criteria/

If No, please complete template. If yes please go to Q34 & 35.

For NGS panel tests, please complete a form for each clinical entry point/subpanel as described in Q2

Please contact the UKGTN office if you are unsure whether testing criteria is available.

34. If there is previously approved Testing Criteria that you agree to, please list below and transcribe in to this submission. If for NGS sub panels please state the sub panel that the Testing Criteria is to be used for.

Cockayne Syndrome

http://ukgtn.nhs.uk/uploads/tx_ukgtn/CSA_CSB_ERCC8_ERCC6_TC_Sept_12.pdf

Peroxisome 24 Gene Panel

http://ukgtn.nhs.uk/uploads/tx_ukgtn/Peroxisome_Disorders_24_Gene_Panel_TC_Mar15.pdf

35.

If there is previously approved Testing Criteria that you do not agree to, please submit revised Testing Criteria in this Gene Dossier and list below where the Testing Criteria replaces current criteria.

Current Testing Criteria Name **(insert link from UKGTN website to the current Testing Criteria i.e. open the Testing Criteria so it is viewable online and then copy and paste the link from the website e.g** **http://ukgtn.nhs.uk/uploads/tx_ukgtn/ARVC_TC_Oct_09.pdf.)**	**New Testing Criteria Name & sub panel name if applicable** **(include new Testing Criteria in this Gene Dossier)**
Cockayne Syndrome **http://ukgtn.nhs.uk/uploads/tx_ukgtn/CSA_CSB_ERCC8_ERCC6_TC_Sept_12.pdf**	
Peroxisome 24 Gene Panel **http://ukgtn.nhs.uk/uploads/tx_ukgtn/Peroxisome_Disorders_24_Gene_Panel_TC_Mar15.pdf**	

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UKGTN Testing Criteria

Test name: **General Leukodystrophy & Mitochondrial Leukoencephalopathy 96 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Radiologically-identified white matter abnormality (e.g. brain magnetic resonance imaging) **AND**	
Developmental delay	

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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UKGTN Testing Criteria

Test name: **Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease 12 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	
Consultant in Paediatric Metabolic Disease	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
MRI scan showing evidence of hypomyelination (defined as severe deficiency of myelination identified on MRI after the age of 2 years **OR** failure of progression of myelination on successive scans at least 6 months apart, one of which must be after the age of 12 months) **AND**	
Developmental delay **OR** intellectual disability **OR** seizures	

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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UKGTN Testing Criteria

Test name: **Aicardi-Goutieres Syndrome 7 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	
Consultant in Paediatric Metabolic Disease	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria.	**Tick if this patient meets criteria**
Clinical suspicion of AGS: • neonatal abnormal neurology with features suggestive of congenital infection (congenital infection excluded by appropriate investigations) OR • Infantile-onset neurological disorder (including some or all of: irritability, regression, motor disorder, fevers, seizures) **AND**	
Abnormal imaging suggestive of AGS: • CT showing intracranial calcification OR • MRI showing leukoencephalopathy, temporal and/or frontal lobe swelling or atrophy **OR**	
Elevated interferon-alpha in cerebrospinal fluid or blood interferon signature indicative of AGS.	

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.

Approval Date: Sept 2016

Submitting laboratory: Leeds RGC

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UKGTN Testing Criteria

Test name: **Mitochondrial Leukoencephalopathy 33 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria.	**Tick if this patient meets criteria**
Biochemical evidence of mitochondrial disease (such as abnormal blood or CSF lactate, respiratory chain enzyme abnormality etc.) **OR**	
MRI leukoencephalopathy pattern suggestive or consistent with mitochondrial disorder (such as cavitating leukoencephalopathy, Leighs pattern etc.)	

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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UKGTN Testing Criteria

Test name: **Leukoencephalopathy with Vanishing White Matter 5 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Abnormal MRI with pattern consistent with VWM. Diffuse cerebral leukoencephalopathy with or without evidence of rarefaction on FLAIR. **AND**	
Clinical, genetic or biochemical exclusion of metachromatic leukodystrophy, Krabbe disease and X-linked adrenoleukodystrophy.	

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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UKGTN Testing Criteria

Test name: **X-linked Adrenoleukodystrophy 1 Gene Panel**	
Approved name and symbol of disorder/condition(s): Adrenoleukodystrophy; ALD	**OMIM number(s):** **#300100**
Approved name and symbol of gene(s): ATP binding cassette, subfamily D, member 1; ABCD1	**OMIM number(s):** ***300371**

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	
Consultant Adult Neurologist	
Consultant Paediatric Neurologist	
Consultant in Adult Metabolic Disease	
Consultant in Paediatric Metabolic Disease	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Clinical presentation suggestive of X-linked adrenoleukodystrophy or adrenomyeloneuropathy **AND**	
Abnormal very long chain fatty acids (VLCFAs)	

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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UKGTN Testing Criteria

Test name: Cockayne Syndrome 2 Gene Panel	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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	
Consultant Paediatric Neurologist	
Consultant in Paediatric Metabolic Disease	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Growth failure by 2 yrs (usually profound)	
AND Microcephaly by 2 yrs (usually profound)	
AND Progressive neurological dysfunction	
AND Characteristic appearance (eg. thin skin, and/or sunken eyes, and/or stooped posture) **AND ONE OR MORE OF :** Cataracts Pig. Retinopathy S-N hearing loss Contractures Severe dental caries Characteristic radiological findings (eg. thickened calvaria) Skin sensitivity to UV-light (sunlight) Ataxia **OR :** proven affected sibling or son/daughter	

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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UKGTN Testing Criteria

Test name: **Peroxisome Disorders 16 Gene Panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

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 in Paediatric Metabolic Disease	
Consultant Paediatrician	
Consultant Neonatologist	
Consultant Clinical Geneticist	
Consultant Paediatric Neurologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
At least 2 of the following clinical features:	
Hypotonia/developmental delay	
Characteristic facial dysmorphism	
Characteristic x-ray findings (e.g. stippling)	
Retinal dystrophy/sensorineural hearing loss	
Liver dysfunction	
AND	
Increased plasma very long chain fatty acids (VLCFAs) **+/-** Deficient erythrocyte membrane plasmalogens	

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

Approval Date: Sept 2016

Submitting laboratory: Leeds RGC

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IS IT A REASONABLE COST TO THE PUBLIC?

36. Based on experience what will be the national (UK wide) expected activity for requesting this test, per annum, for:

Index cases 50

Family members where mutation is known 50 ***If a NGS panel test, it is recognised that the full panel will not be used to test family members where the familial mutation is known.***

37. If your laboratory does not have capacity to provide the full national need please suggest 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. If you are unable to answer this question please write "unknown".

Laboratory likely to be able to service national need.

38. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that are no longer required to make a diagnosis for index cases where index cases would have the molecular genetic test proposed in this gene dossier at an earlier stage in the pathway. It is the tests/procedures that would be stopped for patients that are eligible for the gene test.
This information will be used to calculate the overall investment / savings required in Q39
Example:
The introduction of a 95 gene panel for syndromic and non syndromic hearing loss would allow those patients who are recognised early enough in their pathway to diagnosis to be offered the genetic test instead of having sequential gene tests for individual genes already available and repeated ECGs, ERGs & renal ultrasounds as part of the diagnostic pathway although these may still be required as part of management after diagnosis.

	Type of test	Cost (£)
Imaging procedures	Repeated MRI scans are often performed when the diagnosis not known (2-5, depending on scenario)	£1500 (for MRI under GA, necessary for most neurologically abnormal infants)
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	1) CSF neurotransmitters 2) Single gene genetic screen	1) £629.71 2) £450-1250 – average £720
Physiological tests (e.g. ECG)	EEG, ERG, VEP	Typically approximately £400
Other investigations/procedures (e.g. biopsy)	Muscle biopsy and mitochondrial investigations	Typically approximately £1200
Associated inpatient stays in the diagnostic pathway	**N/A**	**Variable**
Total cost of tests/procedures to be stopped (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)	**Red highlight =** procedures likely to be stopped altogether. **Orange highlight =** procedures that will still be required if a gene test does not find a pathogenic mutation	**£4,449**
If any of the tests/procedures listed above would be carried out on individuals after having the genetic test because the genetic test did not pick up a pathogenic mutation (i.e. negatives), please indicate the costs for these tests to continue to diagnosis. ***For example a panel test replaces single gene tests that have been included above, but after the panel test an individual that tests negative would not need to have these single gene tests, because the genes were on the NGS panel.***		**£3729** All tests, with the exception of single gene genetic screens (average £720/patient, from internal audit data) may still be undertaken.

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39. Please complete the Excel spread sheet available to download from the UKGTN website to calculate the estimated investment or savings, based on the expected annual activity of index & family cases (Q36 above) and using the information provided in Q38. Please submit this separately.

Number of index cases expected annually	50
Number of family member tests expected annually	50
Cost to provide index case test	£860
Cost to provide family member test	£170
Costs associated with tests/procedures for index cases if the genetic test in this Gene Dossier was not available	£4,449
Costs associated with tests/procedures for index cases that test negative for the genetic test in this Gene Dossier	£3,729
Total annual costs for diagnostic tests prior to introduction of the genetic test submitted for evaluation in this Gene Dossier	£222,450
Total annual costs to provide genetic test	£43,000
	-
Additional savings or investment for 100% pick up rate for index cases	£179,450
Percentage of index cases expected not to find a pathogenic mutation (negatives)	54%
Number of index cases estimated to not find a pathogenic mutation (negatives)	27
Costs or savings to provide additional tests for index cases that test negative	£100,683
Total savings / investment prior to application of marginal reduction if applicable	-£78,767
If a panel test and there are genes on the panel test that are already available on either other panel tests or single gene tests please estimate/suggest a marginal percentage reduction of the investment/savings. If you feel this is NOT applicable please leave this as 0%.	20%
Marginal percentage reduction if applicable applied to the savings/investment	-£15,753
TOTAL SAVINGS / INVESTMENT for tests for INDEX CASES	**-£63,014**
Total costs for family members	£8,500
If family testing is already available for any of the genes on this panel across the Network, please estimate the associated funding for these tests.	£1,500
TOTAL SAVINGS / INVESTMENT for tests for FAMILY MEMBERS	£7,000
ADDITIONAL INVESTMENT / SAVINGS FOR ALL ACTIVITY EXPECTED PER ANNUM	-£56,014

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40. Please indicate the healthcare outcomes that apply to this test after diagnosis. It is recognised that all tests recommended by the UKGTN for NHS service improve clinical management and, if a familial mutation is found, allows for prenatal testing and therefore these are not included in the list below.

Healthcare outcomes	Does this apply to this test?
1. Alerts significant clinical co-morbidities	Yes
2. Reduces mortality/saves lives	Yes
3. Avoids irreversible harm	No
4. Avoids diagnostic procedures/tests (some of which may be invasive) and/or multiple hospital appointments	Yes
5. Avoids incorrect management (e.g. medication or treatment) that could be harmful	Yes
6. Confirms targeted therapy/management	No
7. Earlier diagnosis allowing commencement of treatment earlier with associated improved prognosis	Yes
8. Enables access to educational and social support	Yes
9. At risk family members that test negative for a familial mutation can be discharged from follow up	n/a
10. At risk family members that test positive for a familial mutation have appropriate follow up	n/a

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