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

Submitting laboratory: Manchester 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 appendix 1 listing all of the conditions included using approved OMIM name, symbol and OMIM number.

The **Full Metabolic Panel** contains 226 genes involved in the following 11 areas of clinical/biochemical indication i.e. disorders characterised as:-

1. Lysosomal disorders: includes lysosomal storage disorders, transport defects and protease defects **(LSD).**
2. Neuronal ceroid lipofuscinoses **(NCL).**
3. Peroxisomal biogenesis disorders and disorders of single peroxisomal enzymes **(PER).**
4. Disorders of carbohydrate metabolism: includes glycogenoses, disorders of glucose transport, fructose and galactose metabolism **(CHO).**
5. Organic acidaemias, including disorders of branched chain amino acid catabolism, 3-methylglutaconic acidurias **(OA).**
6. Disorders of amino acid metabolism including phenylketonuria, and cerebral organic acid disorders e.g. glutaric aciduria 1 **(AA).**
7. Fatty acid oxidation defects **(FAOD).**
8. Folate and cobalamin defects, also riboflavin transport defects, and biotin-responsive disorders **(VIT)**
9. Disorders of ketogenesis or ketolysis **(KET).**
10. Disorders of neurotransmission (includes pterins, tyrosinaemia) **(NT).**
11. Disorders associated with hyperammonaemia (includes Urea cycle defects, urea cycle transporter defects **(AMM).**

The testing panel has been sub-divided into 6 sub-panels incorporating the above groups of disorders based on their overlapping clinical and/or biochemical features as follows:
Panel 1. Inborn Errors Of Metabolism (IEM - all 226 genes).
Panel 2. Lysosomal storage disorders and neuronal ceroid lipofuscinosis (LSD & NCL – 50 genes).
Panel 3. Peroxisomal disorders (PER – 23 genes).
Panel 4. Disorders of Carbohydrate metabolism (CHO – 32 genes).
Panel 5. Organic acidaemias and disorders involving cofactors (OA and VIT – 50 genes).
Panel 6. Amino Acid disorders and disorders of Neurotransmission Panel (AA and NT – 43 genes).
Panel 7. Disorders associated with hyperammonaemia, fatty acid oxidation and disorders of ketogenesis or ketolysis (AMM ,FAOD and KET – 38 genes).

See appendix 1 for the full set of genes in each panel.

2. OMIM number for disorder/condition

If a panel test – see 1. Above.

See appendix 1 for OMIM and detailed composition of all 7 panels.

3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences/no more than 50 words) description of how the disorder(s) affect individuals and prognosis.

These are very severe potentially life limiting conditions which can present in a variety of ways. For some of these conditions early diagnosis can offer the opportunity of treatment.

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

The majority of inborn errors of metabolism (IEMs) are due to defects of single genes that code for enzymes that facilitate conversion of substrates into products. For patients with suspected or known

IEMs, successful treatment depends on prompt diagnosis followed by the institution of therapy aimed at metabolic stabilization.

Panel 1. Full Metabolic panel
Sometimes it is strongly suspected that an individual may have a metabolic disorder the exact nature of which is not clear. For example individuals may present with a very severe clinical picture and early death. The clinical suspicion may be of a metabolic disorder but the patient may not survive long enough for enough metabolic investigations to be carried out to ascertain a diagnosis. A wide ranging panel may be the best way of making the diagnosis.

For all the panels below there can be a lot of overlap in the clinical presentations so it can be difficult to distinguish between the different disorders.

Panel 2. Lysosomal storage disorders and neuronal ceroid lipofuscinosis (LSD & NCL panel)
There is considerable local clinical expertise in the management and treatment of LSDs. Although individually rare, lysosomal storage disorders collectively have a frequency of about 1/8000 live births. Symptoms can range from relatively mild to severe life limiting disorders. They can include developmental delay, movement disorders, seizures, dementia, deafness and/or blindness. Some people with lysosomal storage disease have enlarged livers (hepatomegaly) and enlarged spleens (splenomegaly) and/or pulmonary and cardiac problems**.**

The neuronal ceroid lipofuscinoses (NCLs) are a particular group of LSDs forming the most common degenerative brain diseases in childhood. NCLs follow a degenerative disease course characterised by a combination of dementia, epilepsy, and motor decline leading to early death. For most childhood NCLs, a progressive visual failure leading to blindness is also a core feature. As for other LSDs the characteristics of these symptoms can vary and the age of disease onset ranges from birth to young adulthood. There are potential long-term complications which are specific to NCL.

Panel 3. Peroxisomal disorders (PER panel)
These form a highly variable disease group, with varying degrees of severity. They can cause developmental delay, muscle problems, impaired hearing and visions and in the more severe cases are life limiting. This group includes disorders such as Zellweger and Refsum disease.

Panel 4. Disorders of Carbohydrate metabolism (CHO panel)
These disorders can result in hypoglycaemia, hepatomegaly, growth failure, muscle pain and/or abnormal blood biochemistry profile. There are at least 10 different types of glycogen storage disorders, which are classified according to the enzyme affected and an accurate diagnosis is important because it guides the treatment.

Panel 5. Organic acidaemias and disorders involving cofactors (OA and VIT panel)
Organic acidemias are conditions characterised by the accumulation of organic acids in body tissues and fluids, including urine (organic acidurias). Characteristics of the conditions include general malaise, reluctance to feed, breathing problems, vomiting, hypotonia (floppiness) and/or spasticity (stiffness). They can cause severe developmental delay and be life limiting. If the correct diagnosis is made there may be treatment to reduce the complications.

Panel 6. Amino acid disorders and disorders of neurotransmission panel (AA and NT panel)
Amino acid disorders involve an inherited deficiency of an enzyme or transport system that mediates the metabolism of a specific amino acid resulting in the build-up of amino acids and/or by-products of amino acid metabolism in the blood. They often affect the nervous system causing developmental delay and seizures. If undiagnosed or left untreated these conditions can lead to severely compromised neurological function and in some cases early death.

Panel 7. Disorders associated with hyperammonaemia, fatty acid oxidation and disorders of ketogenesis or ketolysis (AMM ,FAOD and KET)
This panel represents another group of very variable disorders presenting at different ages. They can cause very severe problems including severe liver problems possibly needing transplant and severe

neurological complications including seizures. An early diagnosis may allow treatment to reduce complications and reduce the risk of early death.

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.

See Appendix 1

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 appendix 1 listing all of the genes included using approved HGNC name, symbol, number and OMIM number. Please provide subpanel split (described in Q2 above) in appendix 1.

See Appendix 1

6a. OMIM number(s) for gene(s)

If a panel test – see 5. above

See Appendix 1

6b. HGNC number(s) for gene(s)

If a panel test – see 5. above

See Appendix 1

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. Full Metabolic Panel composed of the following 6 overlapping sub-panels Total 226 genes
2. LSD and NCL 50 genes
3. PER 23 genes
4. CHO 32 genes
5. OA and VIT 50 genes
6. AA and NT 43 genes
7. AMM,FAOD and KET 38 genes

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.

GenU H or G dependent on the sub panel

8. Mutational spectrum for which you test including details of known common mutations

(n/a for panel tests)

If this application is for a panel test to be used for different clinical phenotypes and/or various sub panel tests – please contact the team for advice before completing a Gene Dossier

Point mutations and small insertions/deletions are within the scope of the screen. In addition published intronic mutations have been included. This assay has not been validated for the detection of exonic deletions and insertions.

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

Enrichment is performed with a custom design Sure Select custom target enrichment kit (Agilent) for the HiSeq 2500 (Illumina) system, following the manufacturer's protocols. The target enrichment design consists of the coding region of transcripts, including the immediate splice sites (+/-5 bases), for 226 genes associated with metabolic disorders. Emulsion PCR is conducted on the pull down libraries and samples are run in indexed batches on the sequencer. The samples are sequenced using a HiSeq 2500 (Illumina), according to the manufacturer's protocols. All samples (irrespective of panel) undergo the

same enrichment and emulsion PCR. However only reads that map to the respective panel (indicated by the clinical referral) are considered further. Sequence data is mapped with Genome AnalysisToolKitLite-v2.0.39 (GATK) against the hg19 human genome as a reference. Known polymorphisms are subsequently filtered out of the data obtained using bioinformatic analysis

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

Our minimum quality threshold for analysis is that 97% of bases within the region of interest (over all genes) must be covered at 50x. Samples failing this are repeated until the required read depth is achieved. For samples that meet this minimum threshold Sanger backfill is not carried out to fill individual regions of <50x coverage. Regions of low coverage are highlighted in the clinical report if relevant to the clinical indication.

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

No

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

Yes

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.

The assay will be provided by the laboratory

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.

The minimum quality threshold is defined (in section 9b) as a minimum of 50 reads for at least 97% of the region of interest. This information reflects the laboratory protocol if we have a sample where coverage is below 100%. For all samples tested during validation 100% horizontal coverage was achieved for all genes as indicated in appendix 1.

Our bioinformatics analysis uses two standard and complementary methods of calling insertions and deletions:

1) The Genome Analysis Toolkit (GATK; Broad Institute) is a means of detecting indels of up to 10 base pairs in single read and paired end sequencing, although the reliability of calling reduces as the size of the indel increase. GATK is a standard method of calling indels used by most diagnostic labs.
2) Pindel (Genome Institute, Washington University School of Medicine) detects breakpoints of large deletions, medium sized insertions, inversions, tandem duplications and other structural variants from paired end short reads. In practice we find that this calls indels over 6bp.

The GATK method has been used in the MCGM since 2013 to analyse all our targeted panels (approx. 3,000 samples to date). Considering our retinal dystrophy panel (>1,500 samples) we have so far detected 98 indels ranging in size from 1-9bp. We have also detected evidence of a whole gene deletion and a 43bp deletion which was highlighted as a single base pair change using bioinformatics software, but was later shown to be a large deletion by Sanger sequencing. The software has also detected duplications, insertions and indels ranging from 1-4 base pairs.

It has not been possible to rigorously validate the Pindel package (sensitivity) due to a lack of control samples with a suitable range known insertions or deletions. In addition this method does produce a significant number of false calls (specificity). However we limit our analysis to potentially pathogenic variants (exclude intronic variants outside +/- 5bp from canonical splice sites) and only report calls that can be verified by a second method (usually Sanger).

Validation has demonstrated that the assay exceeds the 95% sensitivity. See appended documentation – Validation document 1. Test validation assessed 6 known disease causing mutations across a 4 of genes (4 patients) as well as 1216 SNPs across all genes in 4 Corriell cell line controls. 100% sensitivity (95% CI 99.75-100%) within the region of clinical significance was achieved.

	Previously tested	NGS test concordant results	NGS False negative
Number of patient samples	**4**		
Unique variants (total)	**6**	**6**	**0**
SNV	**4**	**4**	**0**
Indel (1bp to X bp)	**2**	**2**	**0**
CNV	**0**	**-**	**-**

If a reference sample (eg HapMap/CEPH DNA) has been tested please complete this table too:

	Known variants	NGS test concordant results	NGS False negative
Reference sample details	**4**		
Unique variants (total)	**1216**	**1208**	**8**
SNV	**1216**	**1208**	**8**
Indel (1bp to X bp)	**0**	**0**	**-**
CNV	**0**	**0**	**-**

NB The 8 NGS false negative calls were checked by Sanger sequencing and shown to be false positive calls in the reference sample data

	Variant confirmed by other method	NGS False positive
Number of patient samples with a variant detected by NGS	**8**	
Unique variants (total)	**1222**	**0**
SNV	**1220**	**0**
Indel (1bp to X bp)	**2**	**0**
CNV	**0**	-

6 of the variants were confirmed by Sanger sequencing. The remaining 1216 variants were confirmed by comparison to Omni2.5 beadchip array data for the Coriell cell line reference DNA samples.

Since completing this prospective validation we have retrospectively validated the panel with live test samples – we have identified 12 disease causing SNVs and 4 indels all of which were confirmed using Sanger (0 false positives).

12a. Are you providing this test already?

Yes

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

Sanger Based Tests	NGS Based Tests
-	27

The above figures represent reports issued using NGS based tests (confirmed using Sanger).

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

Sanger Based Tests	NGS Based Tests
-	13

The above figures represent reports issued using NGS based tests (confirmed using Sanger).
12d. Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.
October 2014 to present (all within full clinical diagnostic setting).
13a. Is there specialised local clinical/research expertise for this disorder?
Yes
13b. If yes, please provide details
The Willink Biochemical Genetics Unit is part of the Manchester Centre for Genomic Medicine (see: http://www.mangen.co.uk/index.php). Expertise is provided by paediatric metabolic consultants (Dr Simon Jones, Dr Andrew Morris, Dr E Jameson, Dr A Broomfield) and genetic consultants (lead genetic clinician Dr Siddharth Banka). In addition we are supported by adult metabolic consultants at The Mark Holland Metabolic Unit at the Salford Royal Foundation NHS Trust (adult metabolic consultant Dr Chris J Hendriksz).
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.
Not applicable

EPIDEMIOLOGY

15a. Estimated prevalence of conditions in the general UK population

Prevalence is total number of persons with the condition(s) in a defined population at a specific time.

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

Please identify the information on which this is based.

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

It is currently not possible to estimate accurately the prevalence individual IEMs within the UK population as individually they are exceedingly rare, resulting in very small numbers of cases, even in large populations. These low numbers mean that random variation in the incidence is high, and incidence rates and prevalence proportions will have very wide confidence intervals. This is compounded by the fact that many conditions demonstrate marked phenotypic variability which can lead to mistaken diagnosis and the prevalence of many of inborn errors of metabolism (IEMs) vary according to the ethnic background.

15b. Estimated annual incidence of conditions in the general UK population

Incidence is total number of new 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.

For panel tests, please provide for groups of conditions.

The incidence of inborn errors of metabolism (IEMs) as a whole may be more common than was previously estimated with 1 in 800 live births being affected (rather than the often quoted 1 in 2500-5000). For groups of conditions: LSD ~1 in 5000 (LSD +NCL panel); Peroxisomal ~1 in 13,500 (PER panel); Glycogen Storage disorders 1 in 800 (CHO panel); Fatty acid oxidation defects ~1 in 13,000, Urea cycle defects 1 in 22,000 (AMM +FAOD +KET panel); Organic acidaemia ~1 in 8000 (OA+VIT panel); Amino acids excluding PKU 1 in 5,300 (AA and NT panel)[1]. Given the number of live births in the North West of England[2] in 2012 we estimate the incidence of IEMs in the North West region to be approximately 111 new cases a year.

Overall the incidence in UK for the disorders across the full metabolic panel has been estimated at 706 cases per year[3].

1. Sanderson et al Incidence of inherited metabolic disorders in the West Midlands Arch Dis Child 91(11) 896-899 (2006).
2. Office for national Statistics
3. http://www.phgfoundation.org/file/ID/600/

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**

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).

Please see section 11.

Based upon the figures given above (Section 11).

Analytical sensitivity: 1214/1222 = 99.34% (95% CI 98.71-99.72%).

We have not independently confirmed all negative results (variants concordant with the reference sequence) by an independent test hence it is not possible to give an estimate of test specificity.

Exonic deletions and duplications cannot be identified using this test.
Read depth minimum cut off: 50x

	Previously tested	**NGS test concordant results**	**NGS False negative**
Number of patient samples	**4**		
Unique variants (total)	**6**	**6**	**0**
SNV	**4**	**4**	**0**
Indel (1bp to X bp)	**2**	**2**	**0**
CNV	**0**	**-**	**-**

If a reference sample (eg HapMap/CEPH DNA) has been tested please complete this table too:

	Known variants	**NGS test concordant results**	**NGS False negative**
Reference sample details	**4**		
Unique variants (total)	**1216**	**1208**	**8**
SNV	**1216**	**1208**	**8**
Indel (1bp to X bp)	**0**	**0**	**-**
CNV	**0**	**0**	**-**

Specificity X% (X% CI)

	Variant confirmed by other method	NGS False positive
Number of patient samples with a variant detected by NGS	**8**	
Unique variants (total)	**1222**	**0**
SNV	**1220**	**0**
Indel (1bp to X bp)	**2**	**0**
CNV	**0**	-

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?

Given the breadth of these panels it is not currently possible to give an accurate estimate of clinical sensitivity. If the condition can be confirmed at the biochemical level then clinical sensitivity will be approximately 100% (exonic deletions and duplications are extremely rare and not well documented in this range of disorders).

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 for panel tests

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 for panel tests

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.

Accurate diagnosis of IEMs can be challenging because multiple investigations are often needed, which can be invasive (procedures such as biopsies of liver, muscle or skin, lumbar punctures and repeated brain imaging), expensive and have limited availability. This is time consuming and is often distressing to the patient and family. Performing such a series of investigations may also delay the diagnosis, resulting in missing the narrow 'window of opportunity' for treatment in some disorders. The current multi-gene panel has been designed to circumvent these shortcomings.

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.

IEMs are a group of individually rare, genetic disorders that predominantly affect children. Prognosis and treatments differ greatly even within the same group of disorders. An accurate genetic diagnosis is beneficial for timely medical management, genetic counselling of families, carrier testing of relatives, and prenatal testing. However, accurate diagnosis of IEMs can be challenging because multiple investigations are often needed, which can be invasive (procedures such as biopsies of liver, muscle or skin, lumbar punctures and repeated brain imaging), expensive and have limited availability. This is time consuming and is often distressing to the patient and family. Performing such a series of investigations may also delay the diagnosis, resulting in missing the narrow 'window of opportunity' for treatment in some disorders. The current multi-gene panel has been designed to circumvent these shortcomings.

In some instances, a clinical history and biochemical testing may not completely rule out a genetic or a non-genetic cause. In which case the patient may have to undergo a series of tests, sometimes over a period of years during which time accurate counselling about the recurrence risk cannot be given to the family. Therefore even a 'negative' metabolic panel test result will help to significantly reduce the chances of a known genetic cause for a particular phenotype which will save on a long and expensive testing odyssey.

If a metabolic cause of death is suspected at post mortem at this stage it is too late to perform appropriate biochemical tests and so DNA will be the only available course of investigation to pinpoint the genetic cause of a disease within these families.

The proposed panel is designed to supplement the current testing pathway which is extremely complex and heterogeneous and will differ widely depending upon the clinical indication. We envisage significant cost savings in the long term however at the current time these are not possible to estimate accurately. We intend to demonstrate actual cost savings during the course of this service – see later).

Panel 2. Lysosomal storage disorders and neuronal ceroid lipofuscinosis (LSD & NCL panel).
Diagnosis for many LSDs is currently made by demonstration of individual enzyme deficiencies and so this panel will be particularly useful for:

- patients with a suspected storage disease in whom other enzyme testing and single gene analysis has been normal.
- patients with a non-specific "storage-like" presentation who do not fit the typical phenotype for a specific disorder.
- patients with a suspected ultra-rare LSD for which clinical mutation testing is not routinely available

Panel 3. Peroxisomal disorders (PER panel).
PER disorders are genetically extremely heterogeneous and knowing the underlying mutation in a patient with a PER disorder facilitates carrier testing of relatives, early prenatal testing or pre-implantation genetic diagnosis and provides insights into genotype–phenotype correlations, which greatly assists patient management. However there is no comprehensive testing facility in the NHS for

peroxisomal disorders and currently, to identify the underlying mutations in PER disorders, PEX cDNA transfection complementation assays are required in order to prioritise gene testing. The PER panel would replace this time consuming and expensive process.

Panel 4. Disorders of Carbohydrate metabolism (CHO panel).
Currently, a definitive diagnosis is achieved via biopsy of the affected organ or organs which is time consuming and invasive.

Panel 5. Organic acidaemias and disorders involving cofactors (OA and VIT panel).
Specialist referral laboratories (none in the UK) currently undertake lengthy investigations at the metabolite level, genetic complementation analysis and enzymatic studies to allow a definitive classification of this heterogeneous group of disorders and identify the candidate gene which can then be screened for mutations. Reliable classification of these patients is essential for treatment and prenatal analysis. This panel also contains genes associated with vitamin cofactor deficiencies such as folate and cobalamin defects, also riboflavin transport defects, and biotin-responsive disorders, many of which are treatable conditions i.e. vitamin responsive.

Panel 6 Amino acid disorders and disorders of neurotransmission panel (AA and NT panel)
Genetic testing and identification of mutations will enable carrier testing of at risk relatives (particularly important in consanguineous communities) and the possibility of pre-implantation genetic diagnosis.

Panel 7 Disorders associated with hyperammonaemia, fatty acid oxidation and disorders of ketogenesis or ketolysis (AMM ,FAOD and KET).
Investigation of these disorders can be very lengthy and invasive. A panel test should shorten this investigative process.

26. 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.

Families would wait a long time for or never get a diagnosis. Patients could miss the opportunity for treatment which reduces morbidity and mortality. Carrier testing of at risk relatives and prenatal diagnosis would be more difficult as they cannot always be done biochemically and PGD would not be possible.

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 IEMs alternative biochemical tests exist. However, they can be performed only when a specific diagnosis is suspected and appropriate samples are available. Sometimes screening investigations can indicate that a patient has one of the conditions from a particular group of disorders. Even then a series of invasive, expensive and time taking investigations may be needed to get to the accurate diagnosis (e.g. peroxisomal disorders, methylmalonic academia). In most cases even when the biochemical tests can precisely identify the underlying diagnosis, a mutation analysis of the relevant gene is required because to facilitate carrier testing in family members and in many cases, prenatal diagnosis.

28. What unexpected findings could this test show? 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.

We are not aware of any unsolicited secondary findings that this test may uncover (apart from carrier status of other genes in the panel). Interrogation of OMIM for secondary disease associations for the genes in this panel reveals the following list of genetic risk factors i.e. apparently abnormal laboratory results ([]) and mutations that contribute to susceptibility to multifactorial disorders ({ }). We do not consider these to be of significance to the patients being tested and do not intend reporting these results.

Gene	OMIM number	Association
CPS1	608307	{Pulmonary hypertension, neonatal, susceptibility to}
CPS1	608307	{Venoocclusive disease after bone marrow transplantation}
DBH	609312	[Dopamine-beta-hydroxylase activity levels, plasma]
GABRG2	137164	{Epilepsy, childhood absence, susceptibility to, 2}
HEXA	606869	[Hex A pseudodeficiency]
MTHFR	607093	{Schizophrenia, (susceptibility to}
MTHFR	607093	{Vascular disease, susceptibility to}
MTHFR	607093	{Neural tube defects, susceptibility to}
MTHFR	607093	{Thromboembolism,|susceptibility to}
MTRR	602568	{Neural tube defects, folate-sensitive, susceptibility to}
NPC1	607107	{Nasopharyngeal carcinoma 1}
PAH	612349	[Hyperphenylalaninemia, non-PKU mild]
SLC2A1	138140	{Epilepsy, idiopathic generalized, suscpetibility to, 12}
SLC2A2	138160	{Diabetes mellitus, noninsulin-dependent}
SLC6A3	126455	{Nicotine dependence, protection against}

29. Please list any genes where the main phenotype associated with that gene is unrelated to the phenotype being tested by the panel.

None

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

Not applicable

31. 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.

N/A

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

N/A

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

A one year old boy, first child of healthy consanguineous parents, was seen in the Metabolic clinic. At the age of 11 months, he had collapsed at home with a 4-day history of viral gastroenteritis. His blood sugars were found to be between 1.1 and 1.6 mmol/l. He was treated with IM glucagon and IV boluses. Blood ketones were measured around 60-90 min after admission and were 0.9mmol/L with a glucose of 5.1mmol/l. He recovered quickly and maintained his blood sugars well. A urine sample for organic acids and a blood spot for carnitine and acyl carnitine was sent, probably 12h after admission. The acyl carnitine profile show a high C2 carnitine and a borderline C5 carnitine and the organic acids showed significant dicarboxylic aciduria but virtually absent ketones. On examination at the age of one year he was found to have a moderate hepatomegaly.

This presentation suggested a possible disorder of ketone metabolism. However, it was difficult to be certain because the required metabolic investigations were not sent during the hypoglycemic episode. This is not unusual because of the nature of presentation. Usually, clinicians may consider admitting the child, starving the patient and then send samples for a battery of investigations.

Availability of the Manchester Metabolic NGS panel enabled us to directly test the child's DNA for all known disorder of ketone metabolism on the FAOD+KET+AMN sub-panel. This revealed a *HMGCS2* c.430G>T p.(Val144Leu) hom mutation. The benefits of using the NGS-based panel test in this case were –

a) Diagnosis of an extremely rare condition was achieved. *HMGCS2* mutations cause a very rare disorder of HMGCoA Synthase deficiency that has only been described in 8 children from 6 families (Aledo et al 2006; JIMD **29**: 207-211). The biochemical markers of this test are not well established making the diagnosis even more challenging.
b) Significantly short duration from presentation to diagnosis. All children described in the medical literature are older at the time of diagnosis.
c) Provided diagnostic certainty that enables putting appropriate management plans in place for the patient.
d) Provided the family with an option of genetic testing of their future children and other family members.
e) Saved costs of admission for fasting and repeat of metabolic investigations.

UKGTN Testing Criteria

Test name: Inborn errors of metabolism 226 gene panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologist (Adult or Paediatric)	
Consultant Gastroenterologist	
Consultant Metabolic specialists (Adult or Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria-	**Tick if this patient meets criteria**
Clinical phenotype or screening biochemical or haematological testing suggesting an Inborn error of Metabolism included in the list of diseases covered by the panel.	
AND investigations do not suggest a specific metabolic disorder	
OR patient is deceased	

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.

UKGTN Testing Criteria

Test name: Lysosomal storage disorders and Neuronal Ceroid Lipofuscinosis 50 gene panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologists (Adult or Paediatric)	
Consultant Metabolic specialist (Adult & Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier	
Criteria-	**Tick if this patient meets criteria**
Clinical phenotype or radiological signs suggesting a lysosomal storage disorder or neuronal ceroid lipofuscinosis **AND**	
For LSDs - abnormal urine MPS or oligosaccharides screen or white cell enzymes analysis that are not diagnostic **For NCLs** - demonstration of vacuolated lymphocytes, presence of pathological inclusions on tissue biopsies or deficient enzyme activity that are not diagnostic	

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.

UKGTN Testing Criteria

Test name: Peroxisomal Disorders 23 Gene Panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Metabolic Disease	
Consultant Paediatrician	
Consultant Neonatologist	
Consultant Clinical Geneticist	
Consultant 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.

UKGTN Testing Criteria

Test name: Organic Acidaemias and Disorders involving cofactors 50 Gene Panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologist (Adult or Paediatric)	
Consultant Metabolic specialist (Adult or Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria-	**Tick if this patient meets criteria**
Clinical phenotype suggesting an organic acidaemias or disorder involving cofactors **AND**	
abnormal results of urine organic or amino acid screen or anaemia or unexplained deficiency or a specific vitamin that are not diagnostic	

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.

UKGTN Testing Criteria

Test name: Disorders of Carbohydrate Metabolism 32 Gene Panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologist or Gastroenterologist (Adult or Paediatric)	
Consultant Metabolic specialist (Adult or Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria-	**Tick if this patient meets criteria**
Clinical phenotype suggesting a disorder of carbohydrate metabolism **AND**	
Biochemical or haematological testing suggesting a disorder of carbohydrate metabolism including: **Glycogenoses** • characteristic biochemical abnormality • Abnormal liver function • Abnormal muscle physiology/pathology **Galactose metabolism defects** – • characteristic biochemical findings including hypoglycaemia and hyperbilirubinaemia • presence of urinary reducing substances • reduced GALT or GALE activity in erythrocytes **Glucose transport defects** – • demonstration of abnormal CSF: Blood glucose ratio • renal tubular dysfunction.	

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.

UKGTN Testing Criteria

Test name: Disorders associated with Hyperammonaemia & Fatty Acid Oxidation and Disorders of Ketogenesis or Ketolysis 38 gene panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologist (Adult or Paediatric)	
Consultant Metabolic Specialist (Adult or Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Abnormal clinical features including encephalopathy, severe vomiting or loss of consciousness and one of the following:	
• Plasma ammonia >150µmol/L **OR**	
• Biochemical testing results indicative of fatty acid oxidation **OR**	
• Hypoketotic hypoglycaemia or severe ketoacidosis	

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.

UKGTN Testing Criteria

Test name: Amino Acid Disorders and Disorders of Neurotransmission 43 gene panel	
Approved name and symbol of disorder/condition(s): See appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See appendix 1	**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 Neurologist (Adult or Paediatric)	
Consultant Metabolic specialist (Adult or Paediatric)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria-	**Tick if this patient meets criteria**
Clinical phenotype suggesting an amino acid disorder or disorder of neurotransmission **OR**	
Biochemical or Haematological testing suggesting an amino acid disorder or disorder of neurotransmission • abnormal urine or plasma amino acid profile ~~or~~ • abnormal urine organic acid profile ~~or~~ • abnormal CSF neurotransmitter results.	

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.

IS IT A REASONABLE COST TO THE PUBLIC?

37. Based on experience what will be the national (UK wide) activity, per annum, for:

Index cases 100

Family members where mutation is known 150

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. Please provide expected number of tests to inform completion of Q40

38. 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".

We anticipate meeting the expected capacity.

39. 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 if the index case has a definitive molecular genetic diagnosis from the test proposed in this gene dossier.

The panel encompasses phenotypes or conditions that are extremely varied in their incidence, presentation, age of onset, accepted current diagnostic pathways and their availability and cost and consequently potential savings. However we can illustrate the possible savings with the following case study:

A 1 year old child presented with abnormal very long chain fatty acids and a suspected clinical diagnosis of Zellweger syndrome. In a case such as this the usual practice of diagnosis entails cell culture and complementation studies to prioritise genes prior to genetic analysis. The panel offered a significantly cheaper alternative and in this case identified a homozygous *PEX12* mutation, c.604C>T p.(Arg202Ter).

	Type of test	Cost (£)
Imaging procedures		
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	Cell culture and complementation studies.	£2,500
Physiological tests (e.g. ECG)		
Other investigations/procedures (e.g. biopsy)		
Total cost of tests/procedures no longer required (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)		**£2,500**

It is, however not possible to estimate annual savings based upon this individual case report.

40. Based on the expected annual activity of index cases (Q37), please calculate the estimated annual savings/investments based on information provided in Q39.

Number of index cases expected annually	(a)
Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q39)	(b)
Total annual costs pre genetic test submitted for evaluation in this Gene Dossier	(a) x (b) = (c)
Total annual costs to provide genetic test	(a) x cost of genetic testing for index case = (d)
Additional savings/investment for 100% positive rate for index cases	(d) – (c) = (e)
Percentage of index cases estimated to be negative	(f)
Number of index cases estimated to be negative	(f) x number of index cases = (g)
Costs to provide additional tests for index cases testing negative	(g) x (b) = (h)
Total savings/investment for tests for index patient activity	(e) + (h) = (i)
Total costs for family members	Costs for family member test x number of family members expected to test in a year (j)
If there is a genetic test already available and some of the family testing is already being provided, please advise the cost of the family testing already available	Cost for family member testing already available x estimated number of tests for family members already provided (k)
Total costs for family members minus any family member testing costs already provided	(j) – (k) = (l)
Additional costs/savings for all activity expected in a year	(i) + (l) **Cost Neutral**

41. 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. Genetic testing alerts significant clinical co-morbidities	No
2. Reduced mortality/saves lives	Yes
3. Avoids diagnostic invasive procedures/tests and associated in patient episodes	Yes
4. Confirms targeted therapy	Yes
5. Earlier diagnosis avoiding multi hospital appointments /procedures	Yes
6. Avoids irreversible harm	Yes
7. Enables access to educational and social support	No
8. At risk family members that test negative for a familial mutation can be discharged from follow up	Yes (leukodystrophy)
9. At risk family members that test positive have appropriate follow up	Yes

Appendix 1
Genes in panel test and associated conditions including list of sub panels.

Rows highlighted in yellow indicate where the gene was currently being fully analysed in the context of a single separate UKGTN test at the time of submission of the Gene Dossier

OMIM standard name of condition and symbol	Mode of inheritance	OMIM No	HGNC standard name and symbol of the gene	HGNC No	OMIM No	Evidence of association between gene(s) and condition	% of horizontal coverage of gene	MLPA	Comments
Panel 1 Inborn errors of metabolism 226 gene panel (includes all genes and disorders listed below across all the sub panels)									
Panel 2 Lysosomal storage disorders and Neuronal Ceroid Lipofuscinosis 50 gene panel									
Aspartylglucosaminuria	AR	208400	Aspartylglucosaminidase *AGA*	318	613228	PubMed: 11309371	100%	No	Not on UKGTN
Metachromatic Leukodystrophy	AR	250100	Arylsulphatase A ARSA	713	607574	PubMed: 12503099	100%	No	Fully analysed as a single separate UKGTN test
Mucopolysaccharidosis type VI	AR	253200	Arylsulphatase B ARSB	714	611542	PubMed: 11668612	100%	No	Not on UKGTN
Neuronal ceroid lipofuscinosis	AR	No phenotype MIM	Arylsulphatase G ARSG	24102	610008	PubMed: 20679209	100%	No	Not on UKGTN
Farber lipogranulomatosis	AR	228000	N-acylsphingosine amidohydrolase (acid ceramidase) 1 ASAH1	735	613468	PubMed: 11241842	100%	No	Not on UKGTN
Neuronal ceroid lipofuscinosis 3 Batten disease	AR	204200	ceroid-lipofuscinosis, neuronal 3 CLN3	2074	607042	PubMed: 19028667	100%	No	Fully analysed as a single separate UKGTN test
Neuronal ceroid lipofuscinosis 5	AR	256731	ceroid-lipofuscinosis, neuronal 5 CLN5	2076	608102	PubMed: 20052765	100%	No	Analysed as a single gene

									and in a small CLN panel on UKGTN
Neuronal ceroid lipofuscinosis 6	AR	601780	ceroid lipofuscinosis 6 CLN6	2077	606725	PubMed: 12815591	100%	No	Analysed as a single gene and in a small CLN panel on UKGTN
Neuronal ceroid lipofuscinosis 8	AR	600143	ceroid lipofuscinosis 8 CLN8	2079	607837	PubMed: 16570191	100%	No	Analysed as a single gene and in a small CLN panel on UKGTN
1.Nephropathic cystinosis/ Atypical nephropathic cystinosis 2. Late-onset juvenile or adolescent nephropathic cystinosis 3. Ocular nonnephropathic cystinosis	AR	1.219800 2.219900 3.219750	cystinosin, lysosomal cystine transporter CTNS	2518	606272	PubMed: 12825071 PubMed: 10556299, related citations PubMed: 10625078, related citations	100%	No	Fully analysed as a single separate UKGTN test
Galactosialidosis	AR	256540	Cathepsin A CTSA	9251	613111	PubMed: 10944848	100%	No	Fully analysed as a single separate UKGTN test
Neuronal ceroid lipofuscinosis 10	AR	610127	Cathepsin D CTSD	2529	116840	PubMed: 16670177	100%	No	Not on UKGTN
Pycnodysostosis	AR	265800	Cathepsin K CTSK	2536	601105	PubMed: 10491211	100%	No	Available in UKGTN panel test

Neuronal ceroid lipofuscinosis 4, Parry type	AD	162350	DnaJ (Hsp40) homolog, subfamily C, member 5 DNAJC5	16235	611203	PubMed: 21820099	100%	No	Not on UKGTN
Fucosidosis	AR	230000	fucosidase, alpha-L- 1, tissue FUCA1	4006	612280	PubMed: 10094192	100%	No	Not on UKGTN
Glycogen storage disease II	AR	232300	glucosidase, alpha; acid GAA	4065	606800	PubMed: 14695532	100%	No	Available in UKGTN panel tests
Krabbe Disease	AR	245200	galactosylceramidase GALC	4115	606890	PubMed: 7581365	100%	No	Fully analysed as a single separate UKGTN test
Mucopolysaccharidosis IVA	AR	253000	galactosamine (N-acetyl)-6-sulfatase GALNS	4122	612222	PubMed: 10814710	100%	No	Fully analysed as a single separate UKGTN test here in Manchester
Gaucher Disease	AR	608013	glucosidase, beta, acid GBA	4177	606463	PubMed: 8432537	100%	No	Fully analysed as a single separate UKGTN test here in Manchester
Fabry Disease	XLD (variable in females)	301500	galactosidase, alpha GLA	4296	300644	PubMed: 1315715	100%	No	Fully analysed as both a single gene and in cardiomyopathy panels on UKGTN

1.GM1-gangliosidosis, type I 2.GM1-gangliosidosis, type II 3.GM1-gangliosidosis, type III 4.Mucopolysaccharidosis type IVB	AR	1. 230500 2. 230600 3. 230650 4. 253010	galactosidase, beta 1 GLB1	4298	611458	PubMed: 1909089 [PubMed: 12644936 PubMed: 1907800 PubMed: 11511921	100%	No	Fully analysed as a single separate UKGTN test
GM2-gangliosidosis, AB variant	AR	272750	GM2 ganglioside activator GM2A	4367	613109	PubMed: 10364519	100%	No	Not on UKGTN
Sialuria	AD/ sporadic/ (AR)	269921	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase GNE	23657	603824	PubMed: 10330343	100%	No	Not on UKGTN
1.Mucolipidosis II alpha/beta 2.Mucolipidosis III alpha/beta	AR	1. 252500 2. 252600	: N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits GNPTAB	29670	607840	PubMed: 16200072	100%	No	Fully analysed as a single separate UKGTN test
Mucolipidosis III gamma	AR	252605	N-acetylglucosamine-1-phosphate transferase, gamma subunit GNPTG	23026	607838	PubMed: 19370764	100%	No	Not on UKGTN
Mucopolysaccharidosis type IIID	AR	252940	glucosamine (N-acetyl)-6-sulfatase GNS	4422	607664	PubMed: 12573255	100%	No	Not on UKGTN
Mucopolysaccharidosis VII	AR	253220	glucuronidase, beta GUSB	4696	611499	PubMed: 19224584	100%	No	Not on UKGTN
Tay-Sachs disease/ GM2-gangliosidosis, several forms	AR	272800	hexosaminidase A (alpha polypeptide) HEXA	4878	606869	PubMed: 9090523	100%	No	Fully analysed as both a single gene and in an ataxia panel on

									UKGTN
Sandhoff disease, infantile, juvenile, and adult forms	AR	268800	hexosaminidase B (beta polypeptide) HEXB	4879	606873	PubMed: 18758829	100%	No	Fully analysed as both a single gene and in an ataxia panel on UKGTN
Mucopolysaccharidosis type IIIC	AR	252930	heparan-alpha-glucosaminide N-acetyltransferase HGSNAT	26527	610453	PubMed: 20825431	100%	No	Not on UKGTN
Mucopolysaccharidosis type IX	AR	601492	hyaluronoglucosaminidase 1 HYAL1	5320	607071	PubMed: 10339581	100%	No	Not on UKGTN
Mucopolysaccharidosis II	XLR	309900	iduronate 2-sulfatase IDS	5389	300823	PubMed: 12794697,	100%	No	Fully analysed as a single separate UKGTN test
1.Mucopolysaccharidosis IHurler syndrome 2. Hurler/Scheie 3.Scheie	AR	1.607014 2.607015 3.607016	iduronidase, alpha-L- IDUA	5391	252800	For all 3 phenotypes: PubMed: 11735025	100%	No	Fully analysed as a single separate UKGTN test
Cholesteryl ester storage disease/ Wolman disease	AR	278000	lipase A, lysosomal acid, cholesterol esterase LIPA	6617	613497	PubMed: 8617513	100%	No	Fully analysed as a single separate UKGTN test
Alpha-mannosidosis types I and II	AR	248500	mannosidase, alpha, class 2B, member 1 MAN2B1	6826	609458	PubMed: 22161967	100%	No	Not on UKGTN
Beta-mannosidosis	AR	248510	mannosidase, beta A, lysosomal MANBA	6831	609489	PubMed: 18565776	100%	No	Not on UKGTN
Mucolipidosis IV	AR	252650	mucolipin 1 MCOLN1	13356	605248	PubMed: 11845410,	100%	No	Not on UKGTN

Neuronal ceroid lipofuscinosis 7	AR	610951	major facilitator superfamily domain containing 8 MFSD8	28486	611124	PubMed: 19201763	100%	No	Available in UKGTN panel test
1.Kanzaki disease (609242) 2.Schindler disease, type I/ Schindler disease, type III (609241)	AR	1.609242 2.609241	N-acetylgalactosaminidase, alpha-NAGA	7631	104170	PubMed: 11251574 PubMed: 8782044	100%	No	Not on UKGTN
Mucopolysaccharidosis type IIIB	AR	252920	N-acetylglucosaminidase, alpha NAGLU	7632	609701	PubMed: 11153910	100%	No	Fully analysed as a single separate UKGTN test
Sialidosis, type I/ Sialidosis, type II	AR	256550	sialidase 1 (lysosomal sialidase) NEU1	7758	608272	PubMed: 11063730	100%	No	Fully analysed as a single separate UKGTN test
Niemann Pick C typeC1	AR	257220	Niemann-Pick disease, type C1 NPC1	7897	607623	PubMed: 11333381	100%	No	Fully analysed as a single separate UKGTN test here in Manchester
Niemann Pick C Type C2	AR	607625	Niemann-Pick disease, type C2 NPC2	14537	601015	PubMed: 11125141	100%	No	Fully analysed as a single separate UKGTN test here in Manchester

Neuronal ceroid lipofuscinosis 1	AR	256730	palmitoyl-protein thioesterase 1 PPT1	9325	600722	PubMed: 9425237,	100%	No	Fully analysed as a single separate UKGTN test
1.Combined SAP deficiency 2.Gaucher disease, atypical 3.Krabbe disease, atypical 4.Metachromatic leukodystrophy due to SAP-b deficiency	AR	1. 611721 2. 610539 3. 611722 4. 249900	prosaposin PSAP	9498	176801	PubMed: 11309366 PubMed: 17919309 PubMed: 15773042 PubMed: 8554069	100%	No	Not on UKGTN
Mucopolysaccharidisis type IIIA	AR	252900	N-sulphoglucosamine sulphohydrolase SGSH	10818	605270	PubMed: 18407553	100%	No	Fully analysed as a single separate UKGTN test here in Manchester
1.Salla disease 2.Infantile sialic acid storage disorder	AR	1.604369 2.269920	solute carrier family 17 (acidic sugar transporter), member 5 SLC17A5	10933	604322	Both phenotypes: PubMed: 10581036	100%	No	Not on UKGTN
1Niemann-Pick disease, type A 2, type B	AR	1.257200 2. 607616	sphingomyelin phosphodiesterase 1, acid lysosomal SMPD1	11120	607608	Both phenotypes: PubMed: 19405096	100%	No	Not on UKGTN
Multiple sulfatase deficiency	AR	272200	sulphatase modifying factor 1 SUMF1	20376	607939	PubMed: 15146462	100%	No	Not on UKGTN
Neuronal ceroid lipofuscinosis 2	AR	204500	tripeptidyl peptidase I TPP1	2073	607998	PubMed: 20340139	100%	No	Fully analysed as a single separate

									UKGTN test
Panel 3 Peroxisomal Disorders 23 Gene Panel									
Adrenoleukodystrophy/ Adult adrenomyeloneuropathy	XL	300100	ATP-binding cassette, sub-family D (ALD), member 1 ABCD1	61	300371	PubMed: 11748843	100%	No	Fully analysed as a single separate UKGTN test
Peroxisomal acyl-CoA oxidase deficiency	AR	264470	acyl-CoA oxidase 1, palmitoyl ACOX1	119	609751	PubMed: 17458872	100%	No	Not on UKGTN
Rhizomelic chondrodysplasia punctata type 3	AR	600121	alkylglycerone phosphate synthase AGPS	327	603051	PubMed: 21990100	100%	No	Fully analysed as a single separate UKGTN test
Primary hyperoxaluria type 1	AR	259900	alanine-glyoxylate aminotransferase AGXT	341	604285	PubMed: 19479957	100%	No	Fully analysed as a single separate UKGTN test
Alpha-methylacyl-CoA racemase deficiency	AR	614307	alpha-methylacyl-CoA racemase AMACR	451	604489	PubMed: 10655068	100%	No	Not on UKGTN
Acatalasemia	AR	614097	Catalase CAT	1516	115500	PubMed: 2308162	100%	No	Not on UKGTN
Lethal encephalopathy due to defective mitochondrial peroxisomal fission	AD	614388	dynamin 1-like DNM1L	2973	603850	PubMed: 17460227	100%	No	Not on UKGTN
Rhizomelic chondrodysplasia punctata type 2	AR	606664	glyceronephosphate O-acyltransferase GNPAT	4416	602744	PubMed: 21990100	100%	No	Fully analysed as a single separate

									UKGTN test
D-bifunctional protein deficiency	AR	261515	hydroxysteroid (17-beta) dehydrogenase 4 HSD17B4	5213	601860	PubMed: 16385454	100%		Not on UKGTN
1.Peroxisome biogenesis disorder 1A (Zellweger) 2.Peroxisome biogenesis disorder 1B (NALD/IRD)	AR	1.214100 2.601539	peroxisomal biogenesis factor 1 PEX1	8850	602136	PubMed: 9539740 PubMed: 9398847	100%	No	Fully analysed as a single separate UKGTN test
1.Peroxisome biogenesis disorder 6A (Zellweger) 2.Peroxisome biogenesis disorder 6B	AR	1. 614870 2.614871	peroxisomal biogenesis factor 10 PEX10	8851	602859	PubMed: 9700193 PubMed: 9683594	100%	No	Available in UKGTN small panel test
1.Peroxisome biogenesis disorder 3A (Zellweger) 2.Peroxisome biogenesis disorder 3B	AR	1. 614859 2. 266510	peroxisomal biogenesis factor 12 PEX12	8854	601758	PubMed: 9090384 PubMed: 14571262	100%	No	Available in UKGTN small panel test
1.Peroxisome biogenesis disorder 11A (Zellweger) 2.Peroxisome biogenesis disorder 11B	AR	1.614883 2. 614885	peroxisomal biogenesis factor 13 PEX13	8855	601789	PubMed: 10332040 PubMed: 10441568,	100%	No	Not on UKGTN

1.Peroxisome biogenesis disorder 13A (Zellweger)	AR	614887	peroxisomal biogenesis factor 14 PEX14	8856	601791	PubMed: 15146459,	100%	No	Not on UKGTN
1.Peroxisome biogenesis disorder 8A (Zellweger) 2.Peroxisome biogenesis disorder 8B	AR	1.614876 2.614877	peroxisomal biogenesis factor 16 PEX16	8857	603360	PubMed: 11890679 PubMed: 20647552	100%	No	Not on UKGTN
Peroxisome biogenesis disorder 12A (Zellweger)	AR	614886	peroxisomal biogenesis factor 19 PEX19	9713	600279	PubMed: 20683989	100%	No	Not on UKGTN
1.Peroxisome biogenesis disorder 5A (Zellweger) 2.Peroxisome biogenesis disorder 5B	AR	1.614866 2.614867	peroxisomal biogenesis factor 2 PEX2	9717	170993	PubMed: 14630978 PubMed: 10528859	100%	No	Not on UKGTN
1.Peroxisome biogenesis disorder 7A (Zellweger) 2.Peroxisome biogenesis disorder 7B	AR	1.614872 2.614873	peroxisomal biogenesis factor 26 PEX26	22965	608666	PubMed: 15858711 PubMed: 12851857	100%	No	Available in UKGTN small panel test

Peroxisome biogenesis disorder 10A (Zellweger)	AR	614882	peroxisomal biogenesis factor 3 PEX3	8858	603164	PubMed: 10958759,	100%	No	Not on UKGTN
1.Peroxisome biogenesis disorder 2A (Zellweger) 2.Peroxisome biogenesis disorder 2B	AR	1.214110 2.202370	peroxisomal biogenesis factor 5 PEX5	9719	600414	Both phenotypes PubMed: 7719337	100%	No	Not on UKGTN
1.Peroxisome biogenesis disorder 4A (Zellweger) 2.Peroxisome biogenesis disorder 4B	AR	1.614862 2.614863	peroxisomal biogenesis factor 6 PEX6	8859	601498	PubMed: 8940266 PubMed: 11355018	100%	No	Available in UKGTN small panel test
1.Peroxisome biogenesis disorder 9B 2.Rhizomelic chondrodysplasia punctata, type 1	AR	1.614879 2.215100	peroxisomal biogenesis factor 7 PEX7	8860	601757	PubMed: 12325024 PubMed: 9090381	100%	No	Fully analysed as a single separate UKGTN test
Refsum disease	AR	266500	phytanoyl-CoA 2-hydroxylase PHYH	8940	602026	PubMed: 10767344	100%	No	Not on UKGTN
Panel 4 Disorders of Carbohydrate Metabolism 32 gene panel									
Glycogen storage disease IIIa/ Glycogen storage disease IIIb	AR	232400	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase AGL	321	610860	PubMed: 17047887	100%	No	Available in UKGTN panel test

Glycogen storage disease XII	AR	611881	aldolase A, fructose-bisphosphate ALDOA	414	103850	PubMed: 8598869	100%	No	Available in UKGTN panel test
Glycogen storage disease XIII	AR	612932	enolase 3 (beta, muscle) ENO3	3354	131370	PubMed: 11506403	100%	No	Available in UKGTN panel test
Epilepsy, progressive myoclonic 2A (Lafora)	AR	254780	epilepsy, progressive myoclonus type 2A, Lafora disease (laforin) EPM2A	3413	607566	PubMed: 14722920	100%	No	Available in UKGTN panel test
Fructose-1,6-bisphosphatase deficiency	AR	229700	fructose-1,6-bisphosphatase 1 FBP1	3606	611570	PubMed: 12126934	100%	No	Available in UKGTN panel test
Glycogen storage disease Ia	AR	232200	glucose-6-phosphatase, catalytic subunit G6PC	4056	613742	PubMed: 10748407	100%	No	Available in UKGTN panel test
Dursun syndrome/AR severe congenital neutropenia	AR	612541	glucose 6 phosphatase, catalytic, 3 G6PC3	24861	611045	PubMed: 20799326	100%	No	Not on UKGTN
Galactose epimerase deficiency	AR	230350	UDP-galactose-4-epimerase GALE	4116	606953	PubMed: 9700591	100%	No	Not on UKGTN
Galactokinase deficiency with cataracts	AR	230200	galactokinase 1 GALK1	4118	604313	PubMed: 10790206	100%	No	Not on UKGTN
Galactosaemia	AR	230400	galactose-1-phosphate uridylyltransferase GALT	4135	606999	PubMed: 11261429	100%	No	Fully analysed as a single separate UKGTN test
Glycogen storage disease IV	AR	232500	glucan (1,4-alpha-), branching enzyme 1 GBE1	4180	607839	PubMed: 8613547	100%	No	Available in UKGTN panel test
Glycogen storage disease XV	AR	613507	glycogenin 1 GYG1	4699	603942	PubMed: 20357282	100%	No	Available in UKGTN panel test
Glycogen storage	AR	611556	glycogen synthase 1 (muscle) GYS1	4706	138570	PubMed:	100%	No	Available in

disease 0, muscle						17928598			UKGTN panel test
Glycogen storage disease 0, liver	AR	240600	glycogen synthase 2 (liver) GYS2	4707	138571	PubMed: 9691087	100%	No	Available in UKGTN panel test
Danon disease	AR	300257	lysosomal-associated membrane protein 2 LAMP2	6501	309060	PubMed: 10972294	100%	No	Available in UKGTN panel test
Glycogen storage disease XI	AR	612933	lactate dehydrogenase A LDHA	6535	150000	PubMed: 1953713	100%	No	Available in UKGTN panel test
Epilepsy, progressive myoclonic 2B (Lafora)	AR	254780	NHL repeat containing E3 ubiquitin protein ligase 1 NHLRC1	21576	608072	PubMed: 12958597	100%	No	Available in UKGTN panel test
Glycogen storage disease VII	AR	232800	phosphofructokinase, muscle PFKM	8877	610681	PubMed: 7513946	100%	No	Available in UKGTN panel test
Glycogen storage disease X	AR	261670	phosphoglycerate mutase 2 (muscle) PGAM2	8889	612931	PubMed: 8447317	100%	No	Available in UKGTN panel test
Phosphoglycerate kinase 1 deficiency	AR	300653	phosphoglycerate kinase 1 PGK1	8896	311800	PubMed: 19157875	100%	No	Available in UKGTN panel test
Congenital disorder of glycosylation, type It	AR	614921	phosphoglucomutase 1 PGM1	8905	171900	PubMed: 22492991	100%	No	Available in UKGTN panel test
Muscle glycogenosis	AR	300559	phosphorylase kinase, alpha 1 (muscle) PHKA1	8925	311870	PubMed: 7874115	100%	No	Available in UKGTN panel test
Glycogen storage disease, type IXa1/ Glycogen storage disease, type IXa2	AR	306000	phosphorylase kinase, alpha 2 (liver) PHKA2	8926	300798	PubMed: 7847371	100%	No	Available in UKGTN panel test
AR	AR	261750	phosphorylase kinase, beta PHKB	8927	172490	PubMed:	100%	No	Available in

Phosphorylase kinase deficiency of liver and muscle						9402963			UKGTN panel test
Muscle glycogenosis with low phosphorylase kinase activity	AR	300559	phosphorylase kinase, gamma 1 (muscle) PHKG1	8930	172470	PMID: 12825073	100%	No	Available in UKGTN panel test
Glycogen storage disease Ixc	AR	613027	phosphorylase kinase, gamma 2 (testis) PHKG2	8931	172471	PubMed: 8896567	100%	No	Available in UKGTN panel test
Glycogen storage disease of heart, lethal congenital	AR	261740	protein kinase, AMP-activated, gamma 2 non-catalytic subunit PRKAG2	9386	602743	PubMed: 10368461	100%	No	Available in UKGTN panel test
Glycogen storage disease VI	AR	232700	phosphorylase, glycogen, liver PYGL	9725	613741	PubMed: 9529348	100%	No	Available in UKGTN panel test
McArdle disease	AR	232600	phosphorylase, glycogen, muscle PYGM	9726	608455	PubMed: 19251976	100%	No	Available in UKGTN panel test
1. GLUT1 deficiency syndrome 1 2. GLUT1 deficiency syndrome 2	AR	1. 606777 2. 612126	solute carrier family 2 (facilitated glucose transporter), member 1 SLC2A1	11005	138140	1. PubMed: 9462754 2. PubMed: 18451999	100%	No	Fully analysed as both a single gene and in an epilepsy panel on UKGTN
Fanconi-Bickel syndrome	AR	227810	solute carrier family 2 (facilitated glucose transporter), member 2 SLC2A2	11006	138160	PubMed: 11810292	100%	No	Available in UKGTN panel test
1.Glycogen storage disease Ib 2.Glycogen storage disease	AR	1. 232220 2. 232240	solute carrier family 37 (glucose-6-phosphate transporter), member 4 SLC37A4	4061	602671	Both phenotypes PubMed: 9758626	100%	No	Available in UKGTN panel test

Ic									
Panel 5 Organic Acidaemias and Disorders involving cofactors 50 Gene Panel									
Methylmalonic aciduria and homocystinuria, cblJ type	AR	614857	ATP-binding cassette, sub-family D (ALD), member 4 ABCD4	68	603214	PubMed: 22922874	100%	No	Not on UKGTN
Combined malonic and methylmalonic aciduria	AR	614265	acyl-CoA synthetase family member 3 ACSF3	27288	614245	PubMed: 21841779	100%	No	Not on UKGTN
Megaloblastic anemia-1, Norwegian type	AR	261100	amnion associated transmembrane protein AMN	14604	605799	PubMed: 12590260	100%	No	Not on UKGTN
3-methylglutaconic aciduria, type I	AR	250950	AU RNA binding protein/enoyl-CoA hydratase AUH	890	600529	PubMed: 12655555	100%	No	Not on UKGTN
Maple syrup urine disease, type Ia	AR	248600	branched chain keto acid dehydrogenase E1, alpha polypeptide BCKDHA	986	608348	PubMed: 8037208	100%	No	Not on UKGTN
Maple syrup urine disease, type Ib	AR	248600	branched chain keto acid dehydrogenase E1, beta polypeptide BCKDHB	987	248611	PubMed: 14742428	100%	No	Not on UKGTN
Biotinidase deficiency	AR	253260	biotinidase BTD	1122	609019	PubMed: 9158148	100%	No	Not on UKGTN
Methylmalonic aciduria due to transcobalamin receptor defect	AR	613646	CD320 molecule CD320	16692	606475	PubMed: 20524213	100%	No	Available in UKGTN panel test
Megaloblastic anemia-1, Finnish type	AR	261100	cubilin (intrinsic factor-cobalamin receptor) CUBN	2548	602997	PubMed: 21208123,	100%	No	Not on UKGTN
Maple syrup urine disease, type II	AR	248600	dihydrolipoamide branched chain transacylase E2 DBT	2698	248610	PubMed: 2010537	100%	No	Not on UKGTN
Megaloblastic	AR	613839	dihydrofolate reductase	2861	126060	PubMed:	100%	No	Not on

anemia due to dihydrofolate reductase deficiency			DHFR			21310276			UKGTN
Methylmalonic aciduria and homocystinuria, cble/g type		No OMIM ref	dihydrofolate reductase-like 1 DHFRL1 (pseudogene)	27309	No OMIM ref	PMID: 21876184	100%	No	Not on UKGTN
3-methylglutaconic aciduria, type V	AR	610198	DnaJ (Hsp40) homolog, subfamily C, member 19 DNAJC19	30528	608977	PubMed: 16055927	100%	No	Not on UKGTN
Neurodegeneration due to cerebral folate transport deficiency	AR	613068	folate receptor 1 (adult) FOLR1	3791	136430	PubMed: 19732866	100%	No	Available in UKGTN ataxia panel test
			folate receptor 2 (fetal) FOLR2	3793	136425	PubMed: 2605182	100%	No	Not on UKGTN
			folate receptor 3 (gammal) FOLR3	3795	602469	PubMed: 2605182	100%	No	Not on UKGTN
Glutamate formiminotransferase deficiency	AR	229100	formimidoyltransferase cyclodeaminase FTCD	3974	606806	PubMed: 12815595	100%	No	Not on UKGTN
Intrinsic factor deficiency	AR	261000	gastric intrinsic factor (vitamin B synthesis) GIF	4268	609342	PubMed: 14695536	100%	No	Not on UKGTN
X-linked mental retardation 3 (methylmalonic acidemia and homocysteinemia, cblX type	XLR	309541	host cell factor C1 HCFC1	4839	300019	PubMed: 24011988	100%	No	Not on UKGTN
Holocarboxylase synthetase deficiency	AR	253270	holocarboxylase synthetase (biotin-(proprionyl-CoA-carboxylase (ATP-hydrolysing)) ligase) HLCS	4976	609018	PubMed: 12124727	100%	No	Not on UKGTN
Isovaleric acidemia	AR	243500	isovaleryl-CoA dehydrogenase IVD	6186	607036	PubMed: 1310317	100%	No	Not on UKGTN

Methylmalonic aciduria and homocystinuria, cblF type	AR	277380	LMBR1 domain containing 1 LMBRD1	23038	612625	PubMed: 19136951	100%	No	Available in UKGTN panel test
3-Methylcrotonyl-CoA carboxylase 1 deficiency	AR	210200	methylcrotonoyl-CoA carboxylase 1 (alpha) MCCC1	6936	609010	PubMed: 11170888	100%	No	Not on UKGTN
3-Methylcrotonyl-CoA carboxylase 2 deficiency	AR	210210	methylcrotonoyl-CoA carboxylase 2 (beta) MCCC2	6937	609014	PubMed: 17968484	100%	No	Not on UKGTN
Methylmalonyl-CoA epimerase deficiency	AR	251120	methylmalonyl CoA epimerase MCEE	16732	608419	PubMed: 16752391	100%	No	Available in UKGTN panel test
Methylmalonic aciduria, vitamin B12-responsive	AR	251100	methylmalonic aciduria (cobalamin deficiency) cblA type MMAA	18871	607481	PubMed: 12438653	100%	No	Available in UKGTN panel test
Methylmalonic aciduria, vitamin B12-responsive	AR	251100	methylmalonic aciduria (cobalamin deficiency) cblB type MMAB	19331	607568	PubMed: 12471062	100%	No	Available in UKGTN panel test
Methylmalonic aciduria and homocystinuria, cblC type	AR	277400	methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria MMACHC	24525	609831	PubMed: 20631720	100%	No	Available in UKGTN panel test
Methylmalonic aciduria and homocystinuria, cblD type	AR	277410	methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria MMADHC	25221	611935	PubMed: 18385497	100%	No	Available in UKGTN panel test
Susceptibility to folate-sensitive Spina bifida		601634	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1 MTHFD1	7432	172460	PubMed: 9611072	100%	No	Not on UKGTN
Homocystinuria due to MTHFR deficiency	AR	236250 601634	methylenetetrahydrofolate reductase (NAD(P)H) MTHFR	7436	607093	PubMed: 10679944	100%	No	Not on UKGTN
Homocystinuria-megaloblastic anemia, cblG complementation	AR	250940 601634	5-methyltetrahydrofolate-homocysteine methyltransferase MTR	7468	156570	PubMed: 3384945	100%	No	Available in UKGTN panel test

type									
Homocystinuria-megaloblastic anemia, cbl E type	AR	236270 601634	5-methyltetrahydrofolate-homocysteine methyltransferase reductase MTRR	7432	602568	PubMed: 9501215	100%	No	Not on UKGTN
Methylmalonic aciduria, mut(0) type	AR	251000	methylmalonyl CoA mutase MUT	7526	609058	PubMed: 15643616	100%	No	Available in UKGTN panel test
1.3-methylglutaconic aciduria, type III 2. Optic atrophy 3 with cataract	AR(AD)	1.258501 2.165300	optic atrophy 3 (autosomal recessive, with chorea and spastic paraplegia) OPA3	8142	606580	PubMed: 11668429 PubMed: 15342707	100%	No	Not on UKGTN
Propionicacidemia	AR	606054	propionyl CoA carboxylase, alpha polypeptide PCCA	8653	232000	PubMed: 9385377	100%	No	Fully analysed as a single separate UKGTN test
Propionic acidemia	AR	606054	propionyl CoA carboxylase, beta polypeptide PCCB	8654	232050	PubMed: 10502773	100%	No	Fully analysed as a single separate UKGTN test
Maple syrup urine disease, mild variant	AR	615135	protein phosphatase, Mg2+/Mn2+ dependent, 1K PPM1K	25415	611065	PubMed: 23086801	100%	No	Not on UKGTN
3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	AR	614739	serine active site containing 1 SERAC1	21061	614725	PubMed: 22683713	100%	No	Not on UKGTN
Thiamine metabolism dysfunction syndrome 2	AR	607483	solute carrier family 19 (thiamine transporter), member 3 SLC19A3	16266	606152	PubMed: 20065143	100%	No	Not on UKGTN
Hereditary folate malabsorption	AR	229050	solute carrier family 46 (folate transporter), member 1 SLC46A1	30521	611672	PubMed: 17446347	100%	No	Not on UKGTN

Riboflavin deficiency	sporadic	615026	solute carrier family 52 (riboflavin transporter), member 1 SLC52A1	30225	607883	PubMed: 21089064	100%	No	Fully analysed as a single separate UKGTN test
Brown-Vialetto-Van Laere syndrome 2	AR	614707	solute carrier family 52 (riboflavin transporter), member 2 SLC52A2	30224	607882	PubMed: 22864630	100%	No	Fully analysed as a single separate UKGTN test
1.Brown-Vialetto-Van Laere syndrome 1 2.Fazio-Londe disease	AR	1. 211530 2. 211500	solute carrier family 52 (riboflavin transporter), member 3 SLC52A3	16187	613350	PubMed: 20206331 PubMed: 21110228	100%	No	Fully analysed as a single separate UKGTN test
Mitochondrial DNA depletion syndrome 5	AR	612073	succinate-CoA ligase, ADP-forming, beta subunit SUCLA2	11448	603921	PubMed: 17301081	100%	No	Available in UKGTN panel test
Mitochondrial DNA depletion syndrome 9	AR	245400	succinate-CoA ligase, alpha subunit SUCLG1	11449	611224	PubMed: 19526370	100%	No	Available in UKGTN panel test
Barth syndrome	XLR	302060	Tafazzin TAZ	11577	300394	PubMed: 8630491	100%	No	Fully analysed as a single separate UKGTN test
Transcobalamin I deficiency with lactoferritin deficiency	AR	189905	transcobalamin I (vitamin B12 binding protein, R binder family) TCN1	11652	189905	PubMed: 12356110	100%	No	Not on UKGTN
Transcobalamin II deficiency	AR	275350	transcobalamin II TCN2	11653	613441	PubMed: 19373259	100%	No	Not on UKGTN
Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	AR	614052	transmembrane protein 70 TMEM70	26050	612418	PubMed: 18953340	100%	No	Not on UKGTN
Panel 6 Amino Acid Disorders and Disorders of Neurotransmission 43 gene panel									
GABA-	AR	613163	4-aminobutyrate aminotransferase	23	137150	PubMed:	100%	No	Not on UKGTN

transaminase deficiency			ABAT			10407778			
Hypermethioninemia with deficiency of S-adenosylhomocysteine hydroxylase	AR	613752	adenosylhomocysteinase AHCY	343	180960	PubMed: 15024124	100%	No	Not on UKGTN
Cutis laxa, autosomal recessive, type III	AR	219150	aldehyde dehydrogenase 18 family, member A1 ALDH18A1	9722	138250	PubMed: 24913064	100%	No	Not on UKGTN
Succinic semialdehyde dehydrogenase deficiency	AR	271980	aldehyde dehydrogenase 5 family, member A1 ALDH5A1	408	610045	PubMed: 14635103	100%	No	Not on UKGTN
Pyridoxine-dependent epilepsy	AR	266100	aldehyde dehydrogenase 7 family, member A1 ALDH7A1	877	107323	PubMed: 16491085	100%	No	Available in UKGTN panel test
Glycine encephalopathy	AR	605899	aminomethyltransferase AMT	473	238310	PubMed: 8005589	100%	No	Fully analysed as a single separate UKGTN test
Canavan disease	AR	271900	aspartoacylase ASPA	756	608034	PubMed: 8023850	100%	No	Fully analysed as a single separate UKGTN test
Homocystinuria, B6-responsive and nonresponsive types/Thrombosis, hyperhomocysteinemic	AR	236200	cystathionine-beta-synthase CBS	1550	613381	PubMed: 10338090	100%	No	Selected exons as a single separate UKGTN test
Cystathioninuria	AR	219500	cystathionine gamma-lyase CTH	2501	607657	PubMed: 12574942	100%	No	Not on UKGTN
D-2-hydroxyglutaric aciduria	AR	600721	D-2-hydroxyglutarate dehydrogenase D2HGDH	28358	609186	PubMed: 16037974,	100%	No	Not on UKGTN
Dopamine beta-	AR	223360	dopamine beta-hydroxylase	2689	609312	PubMed:	100%	No	Not on UKGTN

hydroxylase deficiency	?		DBH			11857564			
Aromatic L-amino acid decarboxylase deficiency	AR	608643	dopa decarboxylase (aromatic L-amino acid decarboxylase) DDC	2719	107930	PubMed: 15079002	100%	No	Not on UKGTN
Tyrosinemia, type I		276700	fumarylacetoacetate hydrolase (fumarylacetoacetase) FAH	3579	613871	PubMed: 8723690	100%	No	Available in UKGTN panel tests
Generalized epilepsy with febrile seizures plus, type 3/Familial febrile seizures 8	AR	611277	gamma-aminobutyric acid (GABA) A receptor, gamma 2 GABRG2	4087	137164	PubMed: 11326275	100%	No	Available in UKGTN panel test
Glutaric aciduria, type I	AR	231670	glutaryl-CoA dehydrogenase GCDH	4189	608801	PubMed: 9711871	100%	No	Fully analysed as a single separate UKGTN test
1.Hyperphenylalaninemia, BH4-deficient, B 2.Dystonia, DOPA-responsive, with or without hyperphenylalaninemia	AR	1.233910 2.128230	GTP cyclohydrolase 1 GCH1	4193	600225	PubMed: 7869202 PubMed: 15753436	100%	No	Selected exons as a single separate UKGTN test
Glycine encephalopathy	AR	605899	glycine cleavage system protein H (aminomethyl carrier) GCSH	4208	238330	PubMed: 11592811	100%	No	Not on UKGTN
Glycine encephalopathy	AR	605899	glycine dehydrogenase (decarboxylating)GLDC	4313	238300	PubMed: 10873393	100%	No	Fully analysed as a single separate UKGTN test
Hereditary hyperekplexia 1, autosomal dominant or	AD/AR	149400	glycine receptor, alpha 1 GLRA1	4326	138491	PubMed: 11702206	100%	No	Fully analysed as a single separate UKGTN test

recessive									
Glycine N-methyltransferase deficiency	AR	606664	glycine N-methyltransferase GNMT	4415	606628	PubMed: 11810299	100%	No	Not on UKGTN
Alkaptonuria	AR	203500	homogentisate 1,2-dioxygenase HGD	4892	607474	PubMed: 19862842	100%	No	Not on UKGTN
1.Hawkinsinuria 2. Tyrosinemia, type III	AD	1.140350 2. 276710	4-hydroxyphenylpyruvate dioxygenase HPD	5147	609695	PubMed: 11073718 PubMed: 10942115	100%	No	Not on UKGTN
L-2-hydroxyglutaric aciduria	AR	236792	L-2-hydroxyglutarate dehydrogenase L2HGDH	20499	609584	PubMed: 19911013	100%	No	Not on UKGTN
Brunner syndrome	XLR	300615	monoamine oxidase A MAOA	6833	309850	PubMed: 8211186	100%	No	Not on UKGTN
Hypermethioninemia, persistent, autosomal dominant, due to methionine adenosyltransferase I/III deficiency/Methionine adenosyltransferase deficiency, autosomal recessive	AD/AR	250850	methionine adenosyltransferase I, alpha MAT1A	6903	610550	PubMed: 10677294	100%	No	Not on UKGTN
N-acetylaspartate deficiency	AR	614063	N-acetyltransferase 8-like (GCN5-related, putative) NAT8L	26742	610647	PubMed: 19807691	100%	No	Not on UKGTN
Gyrate atrophy of choroid and retina with or without ornithinemia	AR	258870	ornithine aminotransferase OAT	8091	613349	PubMed: 1737786	100%	No	Not on UKGTN
Phenylketonuria	AR	261600	phenylalanine hydroxylase PAH	8582	612349	PubMed: 9860305	100%	No	Fully analysed as a single separate

									UKGTN test
Hyperphenylalaninemia, BH4-deficient, D	AR	264070	pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1 alpha PCBD1	8646	126090	PubMed: 9585615	100%	No	Not on UKGTN
Pyridoxamine 5'-phosphate oxidase deficiency	AR	610090	pyridoxamine 5'-phosphate oxidase PNPO	30260	603287	PubMed: 15772097	100%	No	Not on UKGTN
Hyperphenylalaninemia, BH4-deficient, A	AR	261640	6-pyruvoyltetrahydropterin synthase PTS	9689	612719	PubMed: 9222755	100%	No	Not on UKGTN
Hyperphenylalaninemia, BH4-deficient, C	AR	261630	quinoid dihydropteridine reductase QDPR	9752	612676	PubMed: 11153907	100%	No	Not on UKGTN
Early infantile epileptic encephalopathy 3	AR	609304	solute carrier family 25 (mitochondrial carrier: glutamate), member 22 SLC25A22	19954	609302	PubMed: 19780765	100%	No	Available in UKGTN panel test
1.Hyperglycinuria 2. Digenic Iminoglycinuria	Semidom	1.138500 2.242600	solute carrier family 36 (proton/amino acid symporter), member 2 SLC36A2	18762	608331	Both phenotypes PubMed: 19033659	100%	No	Not on UKGTN
Cystinuria	AR/AD	220100	solute carrier family 3 (amino acid transporter heavy chain), member 1 SLC3A1	11025	104614	PubMed: 9768685	100%	No	Available in UKGTN panel test
1.Hartnup disorder 2.Hyperglycinuria 3. Digenic Iminoglycinuria	AR	1.234500 2.138500 3.242600	solute carrier family 6 (neutral amino acid transporter), member 19 SLC6A19	27960	608893	1.PubMed: 15286788 2,3.PubMed: 19033659	100%	No	Not on UKGTN
Infantile parkinsonism-dystonia	AR	613135	solute carrier family 6 (neurotransmitter transporter), member 3 SLC6A3	11049	126455	PubMed: 22279524	100%	No	Not on UKGTN

Lysinuric protein intolerance	AR	222700	solute carrier family 7 (amino acid transporter light chain, y+L system), member 7 SLC7A7	11065	603593	PubMed: 18716612	100%	No	Not on UKGTN
Cystinuria	AR/ AD	220100	solute carrier family 7 (amino acid transporter light chain, bo,+ system), member 9 SLC7A9	11069	604144	PubMed: 15635077	100%	No	Available in UKGTN panel test
Dopa-responsive dystonia due to sepiapterin reductase deficiency (	AR	612716	sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) SPR	11257	182125	PubMed: 15241655	100%	No	Not on UKGTN
Sulphite oxidase deficiency	AR	272300	sulphite oxidase SUOX	11460	606887	PubMed: 12112661	100%	No	Not on UKGTN
Tyrosinemia, type II	AR	276600	tyrosine aminotransferase TAT	11573	613018	PubMed: 1357662	100%	No	Not on UKGTN
Recessive segawa syndrome	AR	605407	tyrosine hydroxylase TH	11782	191290	PubMed: 17696123	100%	No	Not on UKGTN
Panel 7 Disorders associated with Hyperammonaemia & Fatty Acid Oxidation and Disorders of Ketogenesis or Ketolysis 38 gene panel									
Includes Panel 5 genes			IVD MMAA MMAB MMACHC MMADHC MUT PCCA PCCB	Described previously in Panel 5 above					
Includes Panel 6 genes			ABAT AHCY	Described previously in Panel 6 above					
ACAD9 deficiency		611126	acyl-CoA dehydrogenase family, member 9 ACAD9	21497	611103	PubMed: 17564966	100%	No	Not on UKGTN
Deficiency of medium chain	AR	201450	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	89	607008	PubMed: 11409868	100%	No	Fully analysed as a single separate

Acyl-CoA dehydrogenase			ACADM						UKGTN test
Deficiency of short-chain Acyl-CoA dehydrogenase	AR	201470	acyl-CoA dehydrogenase, C-2 to C-3 short chain ACADS	90	606885	PubMed: 18523805	100%	No	Not on UKGTN
VLCAD deficiency	AR	201475	a cyl-CoA dehydrogenase, very long chain ACADVL	92	609575	PubMed: 8845838	100%	No	Not on UKGTN
Alpha-methylacetoacetic aciduria	AR	203750	acetyl-CoA acetyltransferase 1 ACAT1	93	607809	PubMed: 9700610	100%	No	Not on UKGTN
?ACAT2 deficiency	AR	614055	acetyl-CoA acetyltransferase 2 ACAT2	94	100678	PubMed: 8812443	100%	No	Not on UKGTN
Argininemia	AR	207800	arginase 1 ARG1	663	608313	PubMed: 1598908	100%	No	Fully analysed as a single separate UKGTN test
Argininosuccinic aciduria	AR	207900	argininosuccinate lyase ASL	746	608310	PubMed: 17326097	100%	No	Fully analysed as a single separate UKGTN test
Citrullinemia	AR	215700	argininosuccinate synthase 1 ASS1	758	603470	PubMed: 19006241	100%	No	Fully analysed as a single separate UKGTN test
Carbamoylphosphate synthetase I deficiency	AR	237300	carbamoyl-phosphate synthase 1, mitochondrial CPS1	2323	608307	PubMed: 21120950	100%	No	Fully analysed as a single separate UKGTN test
Hepatic CPT deficiency type IA	AR	255120	carnitine palmitoyltransferase 1A (liver) CPT1A	2328	600528	PubMed: 12189492	100%	No	Not on UKGTN
1 Hepatic CPT deficiency type II 2 Lethal neonatal CPT II deficiency 3 Myopathy due to CPT II deficiency	AR	1. 600649 2. 608836 3. 255110	carnitine palmitoyltransferase 2 CPT2	2330	600650	1,2. PubMed: 11477613 3. PubMed: 12410208	100%	No	Fully analysed as a single separate UKGTN test
DECR deficiency	?	616034	2,4-dienoyl CoA reductase 1, mitochondrial DECR1	2753	222745	PubMed: 24847004	100%	No	Not on UKGTN
Glutaric acidemia	AR	231680	electron-transfer-flavoprotein, alpha	3481	608053	PubMed:	100%	No	Not on UKGTN

IIA			polypeptide ETFA			1430199			
Glutaric acidemia IIB	AR	231680	electron-transfer-flavoprotein, beta polypeptide ETFB	3482	130410	PubMed: 12815589	100%	No	Not on UKGTN
Glutaric acidemia IIC known as multiple acyl-CoA dehydrogenase deficiency (MADD)	AR	231680	electron-transferring-flavoprotein dehydrogenase ETFDH	3483	231675	PubMed: 19249206	100%	No	Not on UKGTN
Hyperinsulinism-hyperammonemia syndrome	AD/ sporadic	606762	glutamate dehydrogenase 1 GLUD1	4335	138130	PubMed: 9571255	100%	No	Selected exons as a single separate UKGTN test
1LCHAD deficiency 2 Trifunctional protein deficiency	AR	1 609016 2 609015	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit HADHA	4801	600890	1. PubMed: 7811722 2. PubMed: 7738175	100%	No	Targetted mutation analysis as a single separate UKGTN test
Trifunctional protein deficiency	AR	609015	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit HADHB	4803	143450	PubMed: 12754706	100%	No	Not on UKGTN
HMG-CoA lyase deficiency	AR	246450	3-hydroxymethyl-3-methylglutaryl-CoA lyase HMGCL	5005	613898	PubMed: 11129331	100%	No	Not on UKGTN
HMG-CoA synthase-2 deficiency	AR	605911	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)HMGCS2	5008	600234	PubMed: 11479731	100%	No	Not on UKGTN
N-acetylglutamate synthase deficiency	AR	237310	N-acetylglutamate synthase NAGS	17996	608300	PubMed: 12754705	100%	No	Fully analysed as a single separate UKGTN test
Ornithine transcarbamylase deficiency	XLD	311250	ornithine carbamoyltransferase OTC	8512	300461	PubMed: 11793468	100%	No	Fully analysed as a single separate UKGTN test

Succinyl CoA:3-oxoacid CoA transferase deficiency	AR	245050	3-oxoacid CoA transferase 1 OXCT1	8527	601424	PubMed: 1405472	100%	No	Not on UKGTN
Systemic primary carnitine deficiency	AR	212140	solute carrier family 22 (organic cation/carnitine transporter), member 5 SLC22A5	10969	603377	PubMed: 11715001	100%	No	Not on UKGTN
1 Neonatal-onset citrullinemia type II 2 Adult-onset type II citrullinemia	AR	1.605814 2. 603471	solute carrier family 25 (aspartate/glutamate carrier), member 13 SLC25A13	10983	603859	1. PubMed: 11281457 2. PubMed: 18367750	100%	No	Fully analysed as a single separate UKGTN test
Hyperornithinemiahyperammonemia-homocitrullinemia (HHH)syndrome	AR	238970	solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15 SLC25A15	10985	603861	PubMed: 18978333	100%	No	Not on UKGTN
Carnitine-acylcarnitine translocase deficiency	AR	212138	solute carrier family 25 (carnitine/acylcarnitine translocase), member 20 SLC25A20	1421	613698	PubMed: 15057979	100%	No	Fully analysed as a single separate UKGTN test