University Hospitals Bristol and Weston Metabolic Biochemistry Service

The University Hospitals Bristol and Weston Metabolic, Neuroendocrine and Nutrition (MN&N) laboratory is based at the Bristol Royal Infirmary

The MN&N laboratory provides an acute service for the Bristol Royal Hospital for Children and the Bristol Royal Infirmary for the investigation of suspected inherited metabolic disease. It also provides a regional service for the investigation, diagnosis and monitoring of inherited metabolic disease across the South West. This includes the regional lysosomal storage disorders diagnostic service. The laboratory also provides a local and regional service for the investigation of neuroendocrine tumours, Cushing's syndrome, Cystic Fibrosis and Vitamins.

The routine operating hours are Monday – Friday, 9am – 5.30pm

Address

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Key Contacts

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Test Repertoire

Please see table 1 for a full summary of our routine service including standard turnaround times.

NB: Urgent requests will always be prioritised to obtain results sooner than the routine turnaround times listed below. Please contact the laboratory in advance if urgent analysis is required.

5-HIAA (urine): For the investigation and monitoring of carcinoid syndrome

Carcinoid tumours secrete very high levels of the hormone serotonin, causing the classical symptoms of carcinoid syndrome – flushing, hypotension, and tachycardia.
Serotonin is metabolised to 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in the urine. The amount of this metabolite in the urine can be used to screen for a carcinoid tumour.

Sample Requirements: Urine samples should ideally be collected for 24 hours into acetic acid. Strong acid (e.g. HCl) containers should not be used as 5-HIAA is unstable at pH <2. Single random urine samples collected into plain containers are suitable if acidified immediately after collection (pH 3-5). False positive results may occur if patients have ingested large amounts of foods containing 5-hydroxytryptamine (serotonin), e.g. banana, pineapple, tomato, plum, aubergine, avocado, kiwi, walnuts. Therefore these foods should be avoided for 24 hours prior to sample collection. False negative results may occur with incomplete collections, or due to improperly acidified urine samples.

Amino acids (plasma): A quantitative test for the investigation of primary amino acid disorders

May be included as part of the first line metabolic screen. Ideally samples should be collected during the acute event, prior to treatment, or while the patient is suitably stressed, and on a normal diet.
Please include any relevant drug or dietary history with the request as well as clear clinical details.

Sample Requirements: 200 µL lithium heparin plasma only, separated as soon as possible after collection. Store plasma frozen prior to sending, and send to our laboratory frozen. Please note, serum, EDTA plasma, fluoride oxalate plasma or citrate plasma samples are not suitable for analysis.

Amino acids (urine): Rarely indicated as a first line investigation for an underlying metabolic disorder

Plasma amino acids are the test of choice for investigating most primary amino acid disorders. Some exceptions include: the investigation of renal stones, renal tubular disease/ Fanconi syndrome, mitochondrial disorders, failure to thrive, hypophosphatasia, and primary renal tubular aminoacidopathies (e.g. Lysinuric protein intolerance, cystinuria). Please contact the duty paediatric metabolic biochemist for further information.

Sample Requirements: 2 mL fresh urine, creatinine > 1 mmol/L. Note, bacterial degradation can cause false negative results. Samples should be frozen as soon as possible after collection and sent to our laboratory frozen.
Dilute (creatinine <1 mmol/L) samples will still be analysed and significant results reported. However, normal profiles from dilute samples cannot reliably exclude a metabolic disorder so it is important to obtain a repeat sample as soon as possible.

Amino acids (CSF): A quantitative test primarily for the investigation of non-ketotic hyperglycinaemia (NKH) and serine transporter & biosynthesis defects.

Sample Requirements: 200 µL clear CSF, collected into a plain universal container. Store samples frozen prior to sending. Note samples contaminated with blood will lead to erroneous results. Samples MUST be sent with a paired plasma sample for calculation of the CSF: plasma glycine ratio and full interpretation. Blood-stained samples are not suitable for analysis and will result in falsely elevated CSF amino acid values.

Biotinidase (plasma): For the investigation of biotinidase deficiency

This is a rare, but easily treatable disorder, and should be investigated for in all neonates and infants with any clinical signs including; seizures, hypotonia, ataxia, developmental delay, hearing & vision impairment, alopecia and skin rashes.

Holocarboxylase synthetase deficiency presents similarly, but will not be detected by measurement of biotinidase activity. If this is suspected clinically, please contact our laboratory to discuss further investigations.

Sample Requirements: 100 µL EDTA plasma; must be separated within 6 hours of collection. Store plasma frozen prior to sending, and send to our laboratory frozen. Note, low levels can be seen due to immaturity and liver dysfunction, especially in premature neonates, but will normalise as the baby matures.

Chloride (sweat): For the investigation of Cystic Fibrosis (CF) and monitoring of patients with CF

Sweat collection is performed by specially trained staff from our laboratory. Sweat samples are generally not accepted from outside our own laboratory.

Cortisol (24 hour urine): For the investigation of Cushing's syndrome

In Cushing's syndrome there is overproduction of cortisol, this can be either ACTH-dependent (Cushing's disease) or ACTH-independent. In both forms, serum cortisol levels exceed the binding capacity of cortisol binding proteins, and therefore the free cortisol concentration increases. This increased free cortisol is excreted in the urine, the amount of which can be used as a screening test for Cushing's syndrome.

Useful for patients where overnight dexamethasone suppression test is contraindicated, inconclusive or difficult to perform

Sample Requirements: Urine should be collected into a plain 24 hour urine container; acidified samples are not suitable for analysis. False positive results can occur due to psychological and physical stress, pseudo-Cushing's, and severe obesity. False negative results may be obtained if the urine collection is incomplete. Please ensure urine collection start and end times are clearly labelled.

Cortisol & cortisone (saliva): Primarily for the investigation of Cushing's syndrome and monitoring of known Cushing's patients.

Salivary Cortisol & Cortisone analysis may provide a more convenient method for the investigation of possible Cushing's syndrome than 24 hour urine cortisol. For this test to be useful, patients should have a normal sleep-wake cycle.

Increased cortisol production in Cushing's syndrome exceeds the binding capacity of cortisol binding proteins, and therefore increases the concentration of free cortisol in the blood. This non-protein bound cortisol can freely diffuse into the saliva. In Cushing's syndrome the usual diurnal variation in cortisol excretion is lost, and this can be demonstrated through measurement of salivary cortisol and cortisone ad midnight and early morning (7-9 am).

Sample Requirements: Saliva samples should be collected using our laboratory provided salivette, at midnight and between 7-9 am the following morning. Please ensure samples are properly labelled with accurate sample times. Please contact our laboratory to obtain salivettes.

Erroneous results can be obtained in patients who have disturbed sleep-wake cycles, work night shifts, or collect samples at the incorrect time. Please include details of any medications.

Salivary cortisol may also be used to assess treatment efficacy via a "cortisol day curve". This is usually at the request of a consultant endocrinologist. Use in diagnosing adrenal insufficiency evolving also. Please contact our laboratory to discuss.

Fabry (alpha-galactosidase)

Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme alpha-glaactosidase A. Classically, males present in childhood with acroparathesias, angiokeratomas, sweating abnormalities, corneal clouding and proteinuria. Later, coronorary occlusion and cerebral vascular disease. Variant forms with residual enzyme activity present in males in later adulthood with cardiomyopathy and proteinuria. A renal variant exists presenting with end stage renal disease in adulthood. Female carriers may be clinically affected to varying degrees.

A low alpha-galactosidase A activity is indicative of Fabry disease, and should be confirmed via genetic testing. l Alpha-galactosidase A activity within our unaffected reference range will usually exclude Fabry disease in males, but not in females. If there is a strong clinical suspicion, please contact our laboratory to discuss further investigations.

Sample Requirements: EDTA whole blood (at least 3 mL) to reach the laboratory within 24 hours of collection, Monday to Thursday only. Do not send on Fridays. Please mark the package URGENT – WHITE CELL ENZYMES to ensure the samples are handled appropriately by our reception staff.

Gaucher Screen (beta-glucocerebrosidase)

Gaucher Disease is a lysosomal storage disorder caused by a deficiency of the enzyme beta-glucoserebrosidase. Gaucher disease may present with or without neurological disease (type 2&3, and typ1, respectively), bone disease, hepato(spleno)megaly, anaemia. The waste product, glucocerebroside accumaltes intracellularly, and in particular in activated macrophages, producing the characteristic "gaucher cell" appearance under microscopy.

The Gaucher screen includes measurement of the enzyme beta-glucocerebrosidase in leukocytes, and of plasma chitotriosidase; a marker of macrophage activation that is typically grossly elevated in Gaucher disease. A deficiency in the enzyme with elevated plasma chitotriosidase is indicative of Gaucher disease and should always be confirmed via molecular genetics. Note, there is a common polymoprphism in around 6% of the general population in the chitotriosidase gene leading to undetectable activity, even in patients with Gaucher disease. In those cases, chitotriosidase cannot be used as a marker of disease.

Sample Requirements: EDTA whole blood (at least 3 mL) to reach the laboratory within 24 hours of collection, Monday to Thursday only. Do not send on Fridays. Please mark the package URGENT – WHITE CELL ENZYMES to ensure the samples are handled appropriately by our reception staff.

HVA & VMA (urine): For the investigation and monitoring of neuroblastoma

Neuroblastomas are neuroendocrine tumours occurring mostly in infants and young children that excrete the catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic acid (HVA). VMA and HVA can be measured in the urine to screen for neuroblastoma.

The normal excretion of HVA and VMA reduces with age; all results are reported with age-specific reference ranges, however false positives may be obtained in neonates, or patients on the borderline of a reference range. Other false positives may occur due to the effect of severe stress or medications. False negative results may be obtained in very early disease; if clinical suspicion remains, we advise a repeat measurement.

Sample Requirements: Urine samples may be a single random collection, or 24 hour collection into plain or acidified containers.

This test is not routinely available for patients >16 years of age. Please contact the laboratory in advance if you wish to measure HVA/VMA in patients >16 years of age.

Lysosomal enzyme studies

Lysosomal storage disorders are a group of inherited metabolic diseases caused by specific enzyme deficiencies leading to accumulation of waste product in the lysosome.
The standard lysosomal enzyme screen tests for 13 lysosomal storage disorders. Plasma chitotriosidase is also included in the standard screen as a marker of macrophage activation, which can be seen in some lysosomal storage disorders, other inherited metabolic disorders, and some non-metabolic disorders.
Testing for just Gaucher disease or Fabry disease can be requested separately. Note these are not part of the lysosomal enzyme screen.
Please see the table 1 for the complete list of disorders included in the lysosomal enzyme screen. Please give clear clinical details so that the most appropriate tests can be performed.

Sample Requirements: EDTA whole blood (at least 3 mL) to reach the laboratory within 24 hours of collection, Monday to Thursday only. Do not send on Fridays. Please mark the package URGENT – WHITE CELL ENZYMES to ensure the samples are handled appropriately by our reception staff.

Mucopolysaccharidosis, MPS screen (urine)

The mucopolysaccharidoses are a group of lysomomal storage disorders characterised by the accumulation of glycosanimnoglycans, which are subsequently excreted in the urine. The glycosaminoglycan (GAG)/ creatinine ratio is the first line screening test for MPS disorders; 2D GAG electrophoresis will then be reflexed by the laboratory when required. Attenuated forms may be difficult to detect by urine screening, in which case if there remains a high index of clinical suspicion it may be necessary to proceed to enzyme testing.

Dilute or insufficient samples can result in false negatives, and therefore in these cases a repeat sample will be requested initially. However, all samples will be analysed and an amended report will be issued if there are any significant findings. False positives may occur due to sample contamination, e.g. with heparin therapy. Please include any relevant drug or dietary history with the request.

The urine MPS screen and 2D-GAG electrophoresis are screening tests for MPS disorders. An abnormal finding must be confirmed via enzymology and/or genetics. A normal screen may not exclude an attenuated form of an MPS disorder. If there remains a clinical suspicion after a normal MPS screen result, please contact the duty paediatric and metabolic biochemist to discuss further investigations.

Sample Requirements: Fresh urine (at least 5 mL), creatinine > 1 mmol/L. Urine samples should be kept refrigerated and sent to our laboratory as soon as possible after collection. Note – bacterial degradation can cause false negative results. If there is a delay we would recommend freezing the specimen before transit to our laboratory.

MPS enzymes

A confirmatory test to elucidate the MPS subtype after a positive urine MPS screen and/or to definitively exclude a MPS disorder if there is a high index of clinical suspicion.

Our laboratory offers enzyme analysis for MPS type I, II, IIIa, IIIb, VI and VII. However, we advise a urine MPS screen with 2D electrophoresis should be performed in the first instance when an MPS disorder is suspected.
Enzyme analysis may be requested alongside the urine screen if there is a positive family history and/or genetic evidence of a particular MPS disorder. However, the urine screen will be performed prior to enzyme analysis. Please contact the laboratory in advance if sending samples for MPS enzyme analysis.

Sample Requirements: EDTA whole blood (at least 3 mL) to reach the laboratory within 24 hours of collection, Monday to Thursday only. Do not send on Fridays. Please mark the package URGENT – MPS ENZYMES to ensure the samples are handled appropriately by our reception staff.

Organic acids (urine): A qualitative screening test for the investigation of primary organic acidurias

Urine organic acids should be performed as a first line investigation in patients with suspected metabolic disease. Ideally the urine sample should be collected during the acute event, prior to treatment or while the patient is otherwise suitably stressed.

Dilute or insufficient samples can result in organic acids being missed, and therefore a repeat sample will be requested initially. However, all samples will be analysed and an amended report will be issued if there are any significant findings. **Therefore, please still send dilute/ insufficient samples as these can be important diagnostically.**
Please include any relevant drug or dietary history with the request, as well as clear clinical details.

Sample Requirements: 2 mL fresh urine, creatinine > 1.0 mmol/L. Urine samples should be kept refrigerated and sent to our laboratory as soon as possible after collection. Note - bacterial degradation can cause false negative results. If there is a delay we would recommend freezing the specimen before transit to our laboratory.

Total homocysteine (plasma): For the diagnosis, exclusion or monitoring of cases of homocystinuria (classical or due to cobalamin metabolism disorders or folate cycle disorders), molybdenum cofactor or sulphite oxidase deficiency, and can be useful to assess B12 or folate status.

Please include any relevant drug or dietary history with the request as well as clear clinical details.

Sample Requirements: 200 µL EDTA plasma, sSample must be sent to the laboratory chilled on ice, and the plasma separated and frozen within 30 minutes of collection.

Store plasma frozen prior to sending, and send to our laboratory frozen.

Vitamin A&E: Primarily for the investigation of suspected vitamin deficiencies, monitoring of patients on special diets or with malabsorption

Sample Requirements: Serum or lithium heparin plasma samples are acceptable. If not sending immediately, samples can be kept refrigerated for up to 3 days.

TEST	SAMPLE REQUIREMENTS	TECHNIQUE	TURNAROUND TIME (working days)
5-HIAA (urine)	24 hour urine collection (acetic acid)	HPLC	10
Amino acids (plasma)	200 µL Lithium Heparin plasma	Ion exchange chromatography (Biochrom)	10
Amino acids (urine)	2 mL random urine	Ion exchange chromatography (Biochrom)	10
Amino acids (CSF)	200 µL CSF (MUST be sent with paired plasma)	Ion exchange chromatography (Biochrom)	10
Biotinidase	100 µL K-EDTA plasma, separated within 6 hours of collection	Manual enzymatic, fluorometric	10
Chitotriosidase	50 µL plasma. This enzyme is included in our white cell enzyme screen and Gaucher screen.	Manual enzymatic	10
Chloride (sweat)*		Sherwood Chloride meter	1
Cortisol (24 hour urine)	24 hour urine collection (plain)	LC-MS/MS	10
Cortisol & cortisone (saliva)	Saliva collected into salivette available from our laboratory	LC-MS/MS	20

Fabry screen Leukocyte alpha-galactosidase	3 mL EDTA whole blood, to reach laboratory within 24 hours of collection. Do not send on Fridays. Enzyme testing not recommended in females. Genetic testing is the only definitive way to identify heterozygote status.	Manual enzymatic	10
Gaucher screen Plasma chitotriosidase Leukocyte glucocerebrosidase (beta-glucosidase)	3 mL EDTA whole blood, to reach laboratory within 24 hours of collection. Do not send on Fridays.	Manual enzymatic	10
HVA & VMA (urine)	2mL urine (plain)	HPLC	10

Lysosomal enzyme screen Includes testing for the following: Fucosidosis Alpha-Mannosidosis Beta-Mannosidosis Mucolipidosis II/III screen Metachromatic leukodystrophy Krabbe leukodystrophy MPS VII Sandhoff disease Tay-Sachs disease GM1-gangliosidosis Infantile neuronal ceroid lipofuscinosis (CLN1) Late-Infantile neuronal ceroid lipofuscinosis (CLN2) Nieman Pick types A and B Plasma chitotriosidase (lysosomal storage disease screen)	3 mL EDTA whole blood, to reach laboratory within 24 hours of collection. Do not send on Fridays.	Manual enzymatic	20
Mucopolysaccharidosis (MPS)	5 mL random urine	Colourimetric	10

screen			
2D-Glycosaminoglycan electrophoresis		2 dimensional electrophoresis	20
MPS enzymes MPS I MPS II MPS III A MPS III B MPS VI MPS VII	3 mL EDTA whole blood, to reach laboratory within 24 hours of collection. Do not send on Fridays.	Manual enzymatic	5 – 20 (depending on enzymes to be tested)
Organic acids (urine)	2 mL random urine	GC-MS	10
Total homocysteine (plasma)	200 uL EDTA plasma, separated and frozen within 30 minutes	HPLC	10
Vitamins A & E	1 mL serum / lithium heparin plasma	HPLC	10

Table 1 Test repertoire of the MN&N laboratory

*Sweat chloride analysis not available to external users