Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Phenylketonuria (PKU)

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Sample Required
See Sample requirements page at www.nbt.nhs.uk/genetics for full details

Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)
Prenatal testing must be discussed and arranged with the laboratory well in advance.

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

- Phenylketonuria (PKU) is an autosomal recessive disorder, which manifests as hyperphenylalaninemia (HPA) and is the most common error in amino acid metabolism.
- The incidence of PKU in the local population is approximately 1/10,000 with a carrier frequency of approximately 1/50, however there is wide population variation throughout the world and even within the UK.
- PKU is caused by pathogenic variants in the *PAH* gene resulting in deficiency in activity of the hepatic enzyme phenylalanine hydroxylase (PAH) which if left untreated generally leads to irreversible severe physical, neurological and cognitive abnormalities.
- Dietary management from birth leads to normal growth and normal neurological /cognitive development.
- Diagnosis of PKU in neonates is carried out biochemically through the population neonatal screening programme.
- PKU has a broad spectrum phenotype ranging from classical PKU ([Phe] at diagnosis >1200µmol/L) where a strict diet is required to non-PKU HPA ([Phe] at diagnosis 120-480µmol/L) where no dietary restriction is required.
- The *PAH* gene is located at 12q24.1 and has 13 coding exons; it is highly polymorphic. To date over 537 genetic variants have been reported in the *PAH* gene to the PKU knowledgebase.
- Sequencing of the 13 coding exons of the gene would be expected to detect approximately 96.4% of *PAH* pathogenic variants. The vast majority of pathogenic variants are point mutations or small insertions or deletions but single or multiple exon deletions have been described, accounting for ~0.5% of pathogenic variants in the local population, however this may be higher in other populations.
- Establishing the *PAH* genotype of a patient affected with phenylketonuria may be beneficial for two reasons:
  1. It may be possible to predict the severity of the disease as phenotype/genotype correlations have been reported.
  2. It may be possible to give an indication as to whether a patient is responsive to BH4 supplementation as a number of pathogenic variants have been associated with BH4 responsiveness.

Service Offered

- **Diagnostic Testing:** A full *PAH* gene screen in Bristol is offered mainly as confirmation of a biochemical diagnosis. This includes Sanger sequence analysis and MLPA analysis.
- **Carrier Testing:** Testing of parental samples is offered once the familial variant(s) have been identified in the affected offspring.
- **Cascade testing** can subsequently be undertaken on close adult relatives for the identified familial variants(s).
- **Carrier testing for individuals at population risk** can be offered to partners of affected PKU patients or known PKU carriers. A full *PAH* gene screen and MLPA analysis is recommended.
- **Prenatal diagnosis** is not routinely offered but may be carried out if there are adequate clinical grounds and after discussion with the laboratory on a case by case basis.

Target reporting Times

Test	Turn around Time (Calendar days)
Diagnostic screen	42 days
Familial testing for known pathogenic variants	42 days
Urgent Testing (prenatal)	3 days

Please contact the laboratory for current prices

Quality

This laboratory participates in the following external quality assurance schemes which covers this disorder and the techniques used for this service: GENQA PKU scheme (since 2004); EMQN Sanger DNA sequencing scheme (since the pilot scheme was introduced in 2002) and GENQA Pathogenicity of sequence variants interpretation only scheme (pilot scheme introduced in 2012).

Clinical Advice:

If clinical discussion is required we would recommend contact with Dr Germaine Pierre, Paediatric Metabolic Consultant, Bristol Children's Hospital (Tel: 0117 342 1694).
For biochemical testing queries please contact Dr Helena Kemp, Biochemical Genetics, Southmead Hospital, Bristol (Helena.Kemp@nbt.nhs.uk). **Please note,** biochemical carrier testing is now not recommended due to the risk of equivocal results; a full *PAH* gene screen and MLPA analysis is recommended instead.

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