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

FLT3 and *NPM1* biomarker testing in AML

North Bristol NHS Trust

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

Bone marrow – in EDTA, Li Hep or heparinised bone marrow culture media (available from lab)

Blood 2-10 mls in EDTA or Li Hep

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

- In recent years, it has become apparent that there are acquired molecular biomarkers that can give additional prognostic information to patients with acute myeloid leukaemia (AML).

***FLT3*-ITD**

- An internal tandem duplication (ITD) in the juxtamembrane domain of the fms-like tyrosine kinase-3 (*FLT3*) has been found in approximately 25% of adult and 15% of childhood AML.
- The *FLT3*-ITD is an in-frame duplication and tandem insertion of between 3 and 400bp of the juxtamembrane domain-coding sequence leading to a constitutively activated receptor. This causes leukocytosis, a high percentage of bone marrow blast cells, an increased risk of relapse from complete remission and reduced survival.
- *FLT3* mutations are associated with a poor prognosis with patients having an increased relapse risk and a decreased disease free survival (DFS), event free survival (EFS) and overall survival (OS).

NPM1

- Mutations in the nucleophosmin member 1 gene (*NPM1*) have been shown to occur in approximately 35% of patients with AML.
- The most common mutation (Type A) is a duplication of TCTG at position c.956-959 and accounts for 75-80% of cases. Type B (CATG insertion at position c.956-959) accounts for 10% of all cases while Type D (CCTG insertion at position c.956-959) occurs in 5% of all cases. Other mutations are very rare.
- *NPM1* encodes 12 exons and maps to chromosome band 5q35. Mutations of *NPM1* are most commonly restricted to exon 12, although 2 cases have been shown where mutations occurred within exon 9 and 11, respectively. Approximately 40 *NPM1* mutations have been identified in exon 12 so far.
- *NPM1* mutations are associated with a good prognosis with patients having a higher rate of complete remission (CR), longer EFS and a stronger trend to OS than the *NPM1* WT.
- From the MRC AML10/12 trial (Gale *et al.,* 2008) three prognostic groups have been stratified: GOOD (*FLT-3*/ITD-, *NPM1*+), INTERMEDIATE (*FLT-3*/ITD-, *NPM1*- or *FLT-3*/ITD+, *NPM1*+), POOR (*FLT-3*/ITD+, *NPM1*-).

Service Offered

- The Bristol Genetics Laboratory (BGL) is part of the Bristol Haemato-oncology Diagnostic Service (BHODS) and has access to a full range of complementary pathology services.
- Testing for both the *FLT3*-ITD and the *NPM1* exon 12 mutation is carried out on genomic DNA using a duplex PCR and analysed on the ABSciex CEQ8000 Genetic Analysis system.

Referrals

- Referrals are accepted from Consultant Haematologists.

Target reporting Times

- BGL target time: 7 calendar days

Quality

- BGL participates in the UK NEQAS LI EQA programmes for *FLT3* and *NPM1*

Reference: Gale *et al*., (2008) The impact of *FLT3* internal tandem duplication level, number, size and interaction with *NPM1* mutations in a large cohort of young patients with acute myeloid leukaemia. Blood; 111: 2776-2784

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