Quantitative and Qualitative *BCR-ABL1* analysis and kinase domain mutation screening in CML

Contact details:
Bristol Genetics Laboratory
Pathology Sciences
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 414 6168
FAX: 0117 414 6464

Head of Department:
Professor Rachel Butler, FRCPath
Consultant Clinical Scientist

Consultant Lead for Rare Disease:
Maggie Williams, FRCPath

Consultant Lead for Oncology:
Christopher Wragg, FRCPath

Service lead: Jeremy Hancock
Jeremy.Hancock@nbt.nhs.uk

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

5-10ml blood in EDTA. It is important that these samples reach the laboratory within 72 hours of being taken. Any samples received after this time will not be processed as RNA quality cannot be guaranteed.

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

- Chronic myeloid leukaemia (CML) is a myeloproliferative disorder that arises from abnormal pluripotent bone marrow stem cells.
- It is characterised by the presence of a reciprocal translocation between chromosomes 9 and 22 resulting in the formation of a derivative chromosome 22 (the Philadelphia chromosome) and subsequent formation of the *BCR-ABL1* fusion gene.
- The most common transcripts arising from the fusion of the *BCR* and *ABL1* genes are the e13a2 (b2a2), e14a2 (b3a2) and e1a2 transcripts which are used for molecular monitoring of disease in this laboratory.
- Other rarer transcripts have been identified which require bespoke assays for monitoring. Please contact the laboratory if you require any further information on this.
- Molecular monitoring for CML is a vital tool as it allows optimal management of the disease.

Service offered

- BGL is part of the Bristol Haemato-oncology Diagnostic Service (BHODs) and has access to a full range of complementary pathology services.
- Alongside conventional cytogenetic analysis and fluorescent *in situ* hybridisation using *BCR-ABL1* break apart probes, the laboratory offers qualitative reverse transcriptase PCR (RT-PCR), real time quantitative PCR (RQ-PCR) and *ABL1* kinase domain mutation screening.
- RT-PCR is performed on the diagnostic sample and allows for the detection of the *BCR-ABL1* transcripts to identify whether the patient is suitable for RQ-PCR analysis in the laboratory.
- RQ-PCR allows for the molecular monitoring of CML on the international scale of patients with the common e13a2 (b2a2), e14a2 (b3a2) and e1a2 transcripts using the Europe Against Cancer probes and primers outlined in Gabert *et al*., (2003).
- *ABL1* kinase domain mutation screening is offered when a patient is either not optimally responding to therapy or when disease levels begin to rise suggesting a loss of response to therapy.
- RQ-PCR testing, data interpretation and reporting is undertaken as described by Cross *et al.,* (2015) and Foroni *et al*., (2011).
- BGL issues fully interpretive reports using results on the International Scale and in accordance with ELN recommendations for molecular monitoring in CML (Baccarani *et al.,* 2013).
- The main objective of molecular monitoring in CML is to assess the patient response to treatment and to recognise the early signs of relapse.

Referrals

- Diagnostic testing and disease monitoring Target Reporting Time
  - Qualitative Diagnostic Screen — 3 days
  - Quantitative RQ-PCR monitoring — 14 days
  - *ABL1* Kinase domain mutation screen — 28 days

Clinical Advice: If clinical discussion is required, we would recommend contact with your local consultant haematologist

Quality

- BGL participates in the UK NEQAS LI EQA programmes for *BCR-ABL1* RQ-PCR and for *BCR-ABL1* and AML translocations. It also participates in the pilot EQA scheme for AKD mutation screening.

References

- Gabert *et al.,* (2003) Standardization and quality control studies of 'real-time' quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia – A Europe Against Cancer program. *Leukemia*, 17: 2318–2357.
- Foroni *et al.,* (2011) Guidelines for the measurement of *BCR-ABL1* transcripts in chronic myeloid leukaemia. *Br J Haematol;* Apr;153(2):179-90.
- Baccarani *et al.,* (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukaemia. *Blood*; 122(6): 872-884

Information document No.21 Version 14
Active date of this version 17/062019
DETAILS CORRECT AT DATE OF PRINTING ONLY.
Approved by: Jerry Hancock