AWMGS
All Wales Medical Genomics Service

Chronic Myeloid Leukemia (CML) Service

Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) that affects cells of the myeloid lineage.

All CML cases are caused by the Philadelphia chromosome abnormality. This is a reciprocal translocation which leads to a fusion gene by juxtaposition of the ABL1 gene (on chromosome 9) and the BCR gene (on chromosome 22). This results in a faulty tyrosine kinase signaling protein which is constitutionally activated. Treatment of CML has been revolutionized by the development of tyrosine kinase inhibitors (TKIs). Patients receiving TKIs require regular monitoring of the fusion transcript gene to assess response to treatment, this is known as minimal residual disease (MRD) testing.

Test information

- **FISH:** New CML cases are referred for urgent fluorescent in situ hybridization (FISH) testing for the detection of the BCR-ABL1 gene fusion. A positive FISH result confirms the CML diagnosis.
    - G-banding chromosomal analysis is carried out on FISH positive bone marrow samples.

- **Qualitative PCR**: New cases are also tested by a qualitative, diagnostic PCR assay to establish the BCR-ABL1 transcript type. The assay detects the most common CML variants, e13a2 and e14a2 (also referred to as p210 transcripts) both of which occur within the major breakpoint region of the BCR gene and account for 97-98% of CML cases (Foroni et al., 2011). Rarer translocations, involving a variety of BCR exons account for the other 2-3%.
    - In the event of FISH positive, e13a2/e14a2 negative result, the e1a2 (p190) PCR assay will be performed
    - Samples that are FISH BCR-ABL1 positive, e13a2/e14a2 and e1a2 negative may need to be referred for 'rare transcript' testing.

- **MRD***: Samples that are positive for p210 BCR-ABL1 at diagnosis will be eligible for MRD tests to be performed using the p210 qPCR assay.

Referral criteria

Referrals should clearly state if CML is suspected on the request form (request forms that only state BCR-ABL1 will be triaged for molecular testing only).
All requests should be made on an appropriate request form available at the AWMGS website www.medicalgenomicswales.co.uk.

*MRD testing for rare transcripts (FISH BCR-ABL1 positive, e13a2/e14a2 negative) will be referred for 'rare transcript' MRD testing.

Contact Details

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Sample Requirements

Blood/bone marrow in lithium heparin for FISH
Blood in EDTA for PCR
Bone marrow for chromosomal analysis – send in sterile transport medium supplied by laboratory or in a lithium heparin blood tube

Please label samples with three identifiers and date of collection
All samples must be accompanied by a completed request form
Consent for testing and sample storage is assumed when the request is received – it is the responsibility of the referring clinician to ensure that appropriate consent has been obtained

TAT (Calendar days)	
FISH	3 CD
G-banding	21 CD
Qualitative PCR for CML fusion transcripts -	14 CD
Molecular monitoring of BCR/ABL1 transcript levels (quantitative testing – qPCR)	14 CD

References

Foroni et al. Guidelines for the measurement of BCR-ABL1 transcripts in chronic myeloid leukemia. Br J Haematol. 2011 Apr;153(2):179-90