BCR-ABL1 Mutation Analysis for Tyrosine Kinase Inhibitor Resistance

Indications for Ordering

Detect mutations that may impart tyrosine kinase inhibitor (TKI) resistance in either chronic myelogenous leukemia (CML) or Ph+ acute lymphoblastic leukemia (ALL)

Test Description

Next generation sequencing (NGS)

- RNA extracted from whole blood or bone marrow aspirate
- PCR amplification of *BCR-ABL1* SH2, SH3, and kinase domains
- Mutations identified by massively parallel sequencing

Tests to Consider

BCR-ABL1 Mutation Analysis for Tyrosine Kinase Inhibitor Resistance by Next Generation Sequencing 2008420

- Order only for patients with an established diagnosis of a *BCR-ABL1* positive leukemia
- Use to determine if a mutation is present that would interfere with response to TKI therapy in Philadelphia chromosome positive (Ph+) lymphoblastic leukemia or CML
- Detects all common mutations, including T315I
- Higher sensitivity than traditional Sanger sequencing techniques
- Offers coverage of SH2, SH3, and kinase domain
- If 2 mutations are present, this test can potentially determine if they are *cis* or *trans*

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

- Assesses for single gene mutations, including substitutions and insertions and deletions that may have diagnostic, prognostic, and/or therapeutic significance

Related tests

BCR-ABL1, Major (p210), Quantitative 2005017

- Aids in diagnosis and monitoring of individuals with CML or Ph+ ALL who have e13a2 or e14a2 transcripts (p210)

BCR-ABL1, Minor (p190), Quantitative 2005016

- Aids in diagnosis and monitoring of individuals with CML or Ph+ ALL who have e1a2 transcripts (p190)

BCR-ABL1, Qualitative with Reflex to *BCR-ABL1* Quantitative 2005010

- Recommended when submitting initial diagnostic specimen for CML or Ph+ ALL (no previous *BCR-ABL1* testing)
- If qualitative test is positive, the appropriate corresponding quantitative test is performed

Acute Lymphocytic Leukemia (ALL) Panel by FISH, Pediatric 2002719

- Recommended FISH panel in children with newly diagnosed ALL

Chromosome FISH, Interphase 2002298

- Specific FISH probe for t(9;22); *BCR-ABL1* must be requested

Acute Lymphocytic Leukemia (ALL) Panel by FISH, Adult 2002647

- Recommended panel in adults with newly diagnosed ALL

Disease Overview

Treatment issues

CML

- CML is characterized by *BCR-ABL1* translocations
- Initial therapy is TKIs
  - Imatinib (Gleevec) – inhibits tyrosine kinase activity caused by mutant gene
  - Dasatinib (Sprycel) – dual specific SRC/ABL inhibitor
  - Nilotinib (Tasigna) – imatinib derivative with 30-fold potency compared to imatinib
- Resistance to TKIs may result from
  - Acquired point mutations within the ABL kinase domain
  - *BCR-ABL1* amplification
  - Low bioavailability
  - Quiescent CML stem cells
- Resistance may be overcome with
  - Dose adjustments
  - Change in therapy
- Newer drugs may be useful when resistance develops
  - Bosutinib (Bosulif) – dual SRC/ABL inhibitor active in low nanomolar range
  - Ponatinib (Iclusig) –pan *BCR-ABL1* inhibitor (includes T315I mutant inhibition)

- Use of NGS
  - Improves ability to detect low-level clones across larger section of the gene
  - Detection of c*is* clone significantly reduces ability to predict TKI response

ALL

- *BCR-ABL1* mutation is present in subset of ALL
  - More common in adults than children
- Detection of the *BCR-ABL1* mutation is important as it may predict suboptimal response to TKIs

Genetics

Gene – *BCR-ABL1*

Mutations

- Four regions
  - Adenosine triphosphate binding-loop (P-loop) mutations
  - Drug-binding sites
  - Catalytic domain
  - Activation loop
- >70 mutations

Test Interpretation

Results

- Detected – mutation was detected in the SH2, SH3, or kinase domain (ABL1 amino acid residues 46-542)
- Not detected – no mutation detected

Limitations

Negative result does not exclude mutations

- Below the level of detection
- Outside the sequenced region