BCR-ABL1 Mutation Analysis for Tyrosine Kinase Inhibitor Resistance

*BCR-ABL1* mutations may cause resistance to tyrosine kinase inhibitor (TKI) therapy in patients with either chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). Testing should be performed for patients with an established diagnosis of a *BCR-ABL1*-positive leukemia to guide treatment decisions.

**Disease Overview**

**Treatment Issues**

**Chronic Myelogenous Leukemia**
- CML is characterized by *BCR-ABL1* translocations
- Initial treatment protocol is TKI therapy
  - Imatinib (Gleevec) inhibits tyrosine kinase activity caused by the *BCR-ABL1* gene fusion
  - Dasatinib (Sprycel) is a dual specific SRC/ABL inhibitor
  - Nilotinib (Tasigna) is an imatinib derivative with 30-fold potency compared to imatinib
- Resistance to TKI therapy may result from acquired point mutations within the ABL kinase domain, *BCR-ABL1* amplification, low bioavailability, and/or quiescent CML stem cells
  - Resistance may be overcome with dose adjustments or a change in therapy
  - Newer drugs may be useful when resistance develops, including bosutinib (Bosulif) and ponatinib (Iclusig)
- Use of massively parallel sequencing (next generation sequencing) improves the ability to detect low-level clones across larger sections of the gene

**Acute Lymphoblastic Leukemia**

*BCR-ABL1* mutations are present in a subset of ALL patients and are more common in adults than children. Detection of mutations in *BCR-ABL1* is important in helping to determine potential response to TKI therapy.

**Genetics**

**Gene Fusion**

*BCR-ABL1*

**Mutations**
- >130 mutations
- Four regions tested: adenosine triphosphate binding-loop (P-loop), drug-binding sites, catalytic domain, and activation loop

**Test Interpretation**

**Analytical Sensitivity**
- Variant class: single nucleotide variant (SNV)
- Number of variants tested: 396
Positive percent agreement (PPA): 96.3%
PPA, 95% tolerance at 95% reliability: 94.3-98.0%

Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>Mutation detected in the SH2, SH3, or kinase domain (ABL1 amino acid residues 46-542)</td>
</tr>
<tr>
<td>Not amplified</td>
<td>Multiple attempts to amplify the BCR-ABL1 translocation were unsuccessful by PCR</td>
</tr>
<tr>
<td>Not detected</td>
<td>No mutation detected</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction

Limitations

- A negative result does not exclude mutations below the level of detection or outside the sequenced region
- Sensitivity of this assay may be limited, and sequencing may not be possible in patient samples containing low tumor burden (ie, low levels of BCR-ABL1 fusion transcript by international scale % or normalized copy number)
- Not intended to be used for detection or quantification of BCR-ABL1 fusion transcripts

Related Information

- Acute Lymphoblastic Leukemia - ALL
- Chronic Myelogenous Leukemia - CML

Related Tests

- BCR-ABL1, Qualitative with Reflex to BCR-ABL1 Quantitative 2005010
  Method: Reverse Transcription Polymerase Chain Reaction

- BCR-ABL1, Major (p210), Quantitative 2005017
  Method: Quantitative Reverse Transcription Polymerase Chain Reaction

- BCR-ABL1, Minor (p190), Quantitative 2005016
  Method: Quantitative Reverse Transcription Polymerase Chain Reaction

- Acute Lymphocytic Leukemia (ALL) Panel by FISH, Pediatric 2002719
  Method: Fluorescence in situ Hybridization (FISH)

- Acute Lymphocytic Leukemia (ALL) Panel by FISH, Adult 2002647
  Method: Fluorescence in situ Hybridization (FISH)

- Chromosome FISH, Interphase 2002298
  Method: Fluorescence in situ Hybridization (FISH)

- TPMT and NUDT15 3001535
  Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Thiopurine Methyltransferase, RBC 0092066
  Method: Enzymatic/Quantitative Liquid Chromatography-Tandem Mass Spectrometry

- Thiopurine Metabolites by LC-MS/MS 2014484
  Method: Quantitative Liquid Chromatography/Tandem Mass Spectrometry

- Imatinib 3000539
  Method: Immunoturbidimetry