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 Lymphoblastic Leukemia (ALL) Panel by FISH, Pediatric 2002719**
  Method: Fluorescence in situ Hybridization (FISH)

- **Acute Lymphoblastic 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**