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.

Featured ARUP Testing

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

Method: Massively Parallel Sequencing

- 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 Ph+ ALL or CML
  - Detects all common mutations, including T315I
  - Higher sensitivity than traditional Sanger sequencing techniques
  - Offers coverage of SH2, SH3, and kinase domain

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

Result	Interpretation
Detected	Mutation detected in the SH2, SH3, or kinase domain (ABL1 amino acid residues 46-542)
Not amplified	Multiple attempts to amplify the *BCR-ABL1* translocation were unsuccessful by PCR
Not detected	No mutation detected

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
Acute Lymphoblastic Leukemia FISH Panels
BCR-ABL1 (BCR::ABL1) Qualitative and Quantitative Testing
Chronic Myeloid Leukemia - CML
Thiopurine Drug Therapy

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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