# BCR-ABL1 Qualitative and Quantitative Testing

*BCR-ABL1* quantitative testing is recommended for patients with either chronic myelogenous leukemia (CML), a hematopoietic stem cell disease, or acute lymphoblastic leukemia (ALL), an aggressive type of leukemia of either B- or T-lineage immature lymphoid cells. In CML, identification of *BCR-ABL1* fusion genes is used for diagnosis and ongoing therapeutic monitoring. Massively parallel sequencing is used to identify gene mutations that may interfere with the effectiveness of tyrosine kinase inhibitor (TKI) therapy and to determine management strategy. In ALL, *BCR-ABL1* fusion identification is used for risk stratification treatment decisions. Sequencing is used for minimal residual disease (MRD) assessment of Philadelphia chromosome positive (Ph+) ALL.

## Typical Testing Strategy

### Chronic Myelogenous Leukemia

- Bone marrow cytogenetic studies and quantitative reverse transcription polymerase chain reaction (RT-PCR) measurement of *BCR-ABL1* transcript levels recommended before treatment initiation
- Quantitative RT-PCR is used to monitor response to TKI therapy
- *BCR-ABL1* kinase domain mutation analysis (massively parallel sequencing) is useful to monitor TKI therapy and disease progression

### Acute Lymphoblastic Leukemia

- Evaluation for the presence of recurrent genetic abnormalities at diagnosis using karyotyping and/or fluorescence in situ hybridization (FISH) assays
- MRD assessment on bone marrow using flow cytometry and quantitative RT-PCR at the completion of therapy and at regular intervals to monitor progress

## Disease Overview

### Chronic Myelogenous Leukemia

#### Incidence

- 1/555 in the U.S.[1]
  - Represents 15% of all adult leukemias[2]
- Median age of onset is 67 years

### Acute Lymphoblastic Leukemia

#### Incidence

1.58/100,000 in US[3]

- 75-80% of acute leukemias in children
- 20% of adult leukemias

#### Treatment Issues

## Tests to Consider

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

**Method:** Reverse Transcription Polymerase Chain Reaction

- Recommended when submitting initial diagnostic specimen for CML or Ph+ ALL when the BCR-ABL1 fusion form is not known (no previous BCR-ABL1 testing performed) or is unclear
- If qualitative test is positive for the presence of the p210 (major breakpoint), p190 (minor breakpoint), or p230 (micro breakpoint), the corresponding quantitative test is performed

### BCR-ABL1, Major (p210), Quantitative 2005017

**Method:** Quantitative Reverse Transcription Polymerase Chain Reaction

- Appropriate for diagnosis and monitoring of individuals with CML or a subset of B-cell ALL
- BCR-ABL1 major (p210) fusion form is present in almost all cases of CML and in a subset of ALL cases (e13a2 or e14a2 transcripts)

### BCR-ABL1, Minor (p190), Quantitative 2005016

**Method:** Quantitative Reverse Transcription Polymerase Chain Reaction

Useful in cases of Philadelphia chromosome positive (Ph+) ALL to quantify the BCR-ABL1 p190 fusion form

#### Related Tests

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

**Method:** Massively Parallel Sequencing

- Useful for patients with an established diagnosis of a BCR-ABL1 positive (Ph+) leukemia 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
- Provides higher sensitivity than traditional Sanger sequencing techniques

The goal of TKI therapy is to achieve a complete cytogenetic response within 12 months of initiation of therapy with goal of eventual major molecular response. A subset of individuals will eventually achieve a complete molecular response (undetectable *BCR-ABL1* transcripts using a test with 4.5 log sensitivity).

### Prognostic Issues

A 3-log decrease in the level of *BCR-ABL1* fusion transcripts (major molecular response) within 18 months of beginning TKI therapy is an indicator of favorable outcome. Monitoring for recurrence using quantitative measures is crucial for detecting early relapse.

## Genetics

### Gene

*BCR-ABL1*

### Mutations

- >130 mutations
- Four regions tested
  - Adenosine triphosphate binding-loop (P-loop)
  - Drug-binding sites
  - Catalytic domain
  - Activation loop

## Test Interpretation

### *BCR-ABL1*, Major (p210), Quantitative

#### Analytical Sensitivity

1:125,000 normal cells (chart)

#### Results

| Result | Variant(s) Detected | Interpretive Data |
|---|---|---|
| Positive | BCR-ABL1 fusion transcripts (p210) detected | BCR-ABL1/ABL1 quantitative ratio is provided (normalized copy number)<br>Results also reported in terms of BCR-ABL1 international scale (IS) |
| Weakly positive | BCR-ABL1 fusion transcripts detected below the limit of quantitation | BCR-ABL1 to ABL1 ratio cannot be calculated<br>IS result <0.0069% |
| Not detected | No BCR-ABL1 fusion transcripts detected | Does not exclude BCR-ABL1 fusion transcripts (p210) below the test limit of detection<br>Does not exclude BCR-ABL1 fusion transcripts not detected by this test (p190 or p230) |

- Offers coverage of SH2, SH3, and kinase domains

**Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117**

**Method:** Massively Parallel Sequencing

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

**Acute Lymphoblastic Leukemia (ALL) Panel by FISH, Pediatric 2002719**

**Method:** Fluorescence in situ Hybridization (FISH)

Recommended FISH panel for children with newly diagnosed ALL

**Acute Lymphoblastic Leukemia (ALL) Panel by FISH, Adult 2002647**

**Method:** Fluorescence in situ Hybridization (FISH)

Recommended FISH panel for adults with newly diagnosed ALL

**Chromosome FISH, Interphase 2002298**

**Method:** Fluorescence in situ Hybridization (FISH)

- Use to order individual or multiple oncology FISH probes if standard FISH panels are not desired
- The specific probe for t(9;22); BCR-ABL1 must be requested

**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

### Limitation

Does not detect p190.

## BCR-ABL1, Minor (p190), Quantitative

### Analytical Sensitivity

1:125,000 normal cells (chart)s

### Results

| Result | Variant(s) Detected | Interpretive Data |
|---|---|---|
| Positive | BCR-ABL1 fusion transcripts (p210) detected | BCR-ABL1/ABL1 quantitative ratio is provided (normalized copy number) |
| Weakly positive | BCR-ABL1 fusion transcripts detected below the limit of quantitation | BCR-ABL1 to ABL1 ratio cannot be calculated |
| Not detected | No BCR-ABL1 fusion transcripts detected | Does not exclude BCR-ABL1 fusion transcripts (p190) below the test limit of detection<br>Does not exclude BCR-ABL1 fusion transcripts that are not detected by this test (p210 or p230) |

## References


1. National Institutes of Health, U.S. National Library of Medicine. Genetics Home Reference: chronic myeloid leukemia. [Reviewed: Sep 2016; Accessed: Jul 2020]
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: chronic myeloid leukemia, version 3.2020. [Updated: Jan 2020; Accessed: Jul 2020]
3. NCCN Clinical Practice Guidelines in Oncology: acute lymphoblastic leukemia, version 1.2020. National Comprehensive Cancer Network. [Updated Jan 2020; Accessed: Jul 2020]


## Related Information

Acute Lymphoblastic Leukemia - ALL
Chronic Myelogenous Leukemia - CML


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