BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Description
In the treatment of Philadelphia chromosome‒positive leukemias, various nucleic acid‒based laboratory methods may be used to detect the BCR-ABL1 fusion gene for confirmation of the diagnosis; for quantifying mRNA BCR-ABL1 transcripts during and after treatment to monitor disease progression or remission; and for identification of ABL kinase domain single nucleotide variants related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors, or disease progression.

FDA REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT

Chronic Myelogenous Leukemia
BCR-ABL1 qualitative testing for the presence of the fusion gene may be considered medically necessary for the diagnosis of chronic myeloid leukemia (see Policy Guidelines section).

BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines section) may be considered medically necessary for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of ABL kinase domain single nucleotide variants to assess patients for tyrosine kinase inhibitor resistance may be considered medically necessary when there is an inadequate initial response to treatment or any sign of loss of response (see Policy Guidelines section); and/or when there is a progression of the disease to the accelerated or blast phase.
Evaluation of ABL kinase domain single nucleotide variants is considered investigational for monitoring in advance of signs of treatment failure or disease progression.

**Acute Lymphoblastic Leukemia**

*BCR-ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines section) may be considered medically necessary for monitoring of Philadelphia chromosome–positive acute lymphoblastic leukemia treatment response and remission.

Evaluation of ABL kinase domain single nucleotide variants to assess patients for tyrosine kinase inhibitor resistance may be considered medically necessary when there is an inadequate initial response to treatment or any sign of loss of response.

Evaluation of ABL kinase domain single nucleotide variants is considered investigational for monitoring in advance of signs of treatment failure or disease progression.

**POLICY GUIDELINES**

**Diagnosis of Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia**

Qualitative molecular confirmation of the cytogenetic diagnosis (ie, detection of the Philadelphia chromosome) is necessary for accurate diagnosis of chronic myelogenous leukemia (CML). Identification of the Philadelphia chromosome is not necessary to diagnose acute lymphoblastic leukemia (ALL); however, molecular phenotyping is usually performed at the initial assessment (see Determining Baseline RNA Transcript Levels and Subsequent Monitoring subsection).

Distinction between molecular variants (ie, p190 vs p210) is necessary for accurate results in subsequent monitoring assays.

**Determining Baseline RNA Transcript Levels and Subsequent Monitoring**

Determination of *BCR-ABL1* messenger RNA transcript levels should be done by quantitative real-time reverse transcription-polymerase chain reaction–based assays, and reported results should be standardized according to the International Scale.

For CML, testing is appropriate at baseline before the start of imatinib treatment, and testing is appropriate every 3 months when the patient is responding to treatment. After a complete cytogenetic response is achieved, testing is recommended every 3 months for 2 years, then every 3 to 6 months thereafter.

Without a complete cytogenetic response, continued monitoring at 3-month intervals is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib and will likely also be applied to bosutinib and ponatinib (see Rationale section).

For ALL, the optimal timing remains unclear and depends on the chemotherapy regimen used.

**Tyrosine Kinase Inhibitor Resistance**

For CML, inadequate initial response to tyrosine kinase inhibitors (TKIs) is defined as failure to achieve a complete hematologic response at 3 months, only minor cytogenetic response at 6 months, or major (rather than complete) cytogenetic response at 12 months.

Unlike in CML, ALL resistance to TKIs is less well studied. In patients with ALL receiving a TKI, a rise in the *BCR-ABL* mRNA level while in hematologic complete response or clinical relapse warrants variant analysis.
FEP 2.04.85 BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Loss of response to TKIs is defined as hematologic relapse, cytogenetic relapse, or 1-log increase in BCR-ABL1 transcript ratio and therefore loss of major molecular response.

Kinase domain single nucleotide variant testing is usually offered as a single test to identify T315I variant or as a panel (that includes T315I) of the most common and clinically important variants.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HuMan Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals who have suspected CML who receive BCR-ABL1 fusion gene qualitative testing to confirm the diagnosis and establish a baseline for monitoring treatment, the evidence includes validation studies. Relevant outcomes are test accuracy and test validity. The sensitivity of testing with reverse transcription-polymerase chain reaction is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive BCR-ABL1 fusion gene quantitative testing at appropriate intervals during therapy for monitoring treatment response and remission, the evidence includes a randomized trial and case series. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. Studies have shown a high sensitivity of this type of testing and a strong correlation with outcomes, including the risk of disease progression and survival, which may stratify patients to different treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of CML, inadequate initial response, loss of response, and/or disease progression who receive an evaluation for ABL SNVs to assess for TKI resistance, the evidence includes a systematic review and case series. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. The systematic review and case series evaluated pharmacogenetics testing for TKIs and reported the presence of SNVs detected at imatinib failure. These studies have shown a correlation between certain types of variants, treatment response, and the selection of subsequent treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of Ph chromosome-positive ALL who receive BCR-ABL1 fusion gene quantitative testing at baseline before and during treatment to monitor treatment response and remission, the evidence includes a prospective cohort study and case series. Relevant outcomes are test accuracy and validity and medication use. As with CML, studies have shown a high sensitivity for this type of testing and a strong correlation with outcomes, including the risk of disease progression, which may stratify patients to different treatment options. Also, evidence of treatment resistance or disease recurrence directs a change in medication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have Ph chromosome-positive ALL and signs of treatment failure or disease progression who receive an evaluation for ABL1 SNVs to assess for TKI resistance, the evidence includes case series. Relevant outcomes are test accuracy and validity and medication use. Studies have...
shown that specific imatinib-resistant variants are insensitive to one or both of the second-generation TKIs; these variants are used to guide medication selection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) practice guidelines (v.1.2018) on chronic myelogenous leukemia outline recommend methods for diagnosis and treatment management of chronic myelogenous leukemia, including BCR-ABL1 tests for diagnosis, monitoring, and ABL kinase domain single nucleotide variants (see Table 1).5

Table 1. Treatment Recommendations Based on BCR-ABL1 KD SNV Status After Imatinib Treatment Failure

<table>
<thead>
<tr>
<th>Single Nucleotide Variants</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib, omacetaxine, allogeneic HCT, or clinical trial</td>
</tr>
</tbody>
</table>

HCT: hematopoietic cell transplantation; KD: kinase domain; SNV: single nucleotide variant.

The National Comprehensive Cancer Network practice guidelines (v.3.2017) on acute lymphoblastic leukemia (ALL) state that, if minimal residual disease (MRD) is being evaluated, the initial measurement should be performed on completion of induction therapy; additional time points for MRD evaluation may be useful, depending on the specific treatment protocol or regimen used. MRD is an essential component of patient evaluation during sequential therapy.48 Treatment options based on BCR-ABL Mutation Profile are shown in Table 2. The tyrosine kinase inhibitor treatment options for ALL are the same as for chronic myelogenous leukemia.

Table 2. Treatment Recommendations Based on BCR-ABL1 KD SNV Status After Relapsed or Refractory Philadelphia Chromosome−Positive ALL

<table>
<thead>
<tr>
<th>Single Nucleotide Variants</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib</td>
</tr>
</tbody>
</table>

ALL: Acute lymphoblastic leukemia; KD: kinase domain; SNV: single nucleotide variant.

Other
In 2010, technical recommendations for MRD assessment and definitions for response based on MRD results were made to standardize MRD measurements and MRD data reporting in European ALL trials.49

U.S. Preventive Services Task Force Recommendations

Not applicable.
FEP 2.04.85 BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


29. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. *Blood*. Nov 1 2004;104(9):2926-2932. PMID 15256429


FEP 2.04.85  **BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia**


43. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib orNilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-up of the PACE Trial. *American Society of Hematology 54th Annual Meeting, December 2012.* 2012:Abstract 163. PMID


**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2013</td>
<td>New Policy</td>
<td>Policy updated with literature review. References 3, 5, 6, 46-47, 56-57 added. Policy statements added for ALL, medially necessary prior to initiation of treatment, for disease monitoring and to evaluate for TKI resistance. Title also changed to add ALL.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through August 23, 2017; reference 41 added; references 3 and 47 updated. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.