Medical Policy

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

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Policy Number: 612
BCBSA Reference Number: 2.04.85
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

CML
BCR/ABL1 qualitative testing for the presence of the fusion gene may be MEDICALLY NECESSARY for diagnosis of chronic myeloid leukemia.

BCR/ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals during therapy may be MEDICALLY NECESSARY for monitoring of chronic myeloid leukemia treatment response and remission.

Testing is appropriate at baseline before the start of imatinib treatment. Testing is appropriate every 3 months when the patient is responding to treatment. After a complete cytogenetic response is achieved, testing is appropriate every 3 months for 3 years, and then every 3-6 months thereafter. Without attainment of a complete cytogenetic response, continued monitoring at 3-month intervals is recommended.

Evaluation of ABL kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be MEDICALLY NECESSARY when there is inadequate initial response to treatment or any sign of loss of response; and/or when there is progression of the disease to the accelerated or blast phase. Inadequate initial response to tyrosine kinase inhibitors is defined as failure to achieve complete hematologic response at 3 months, only minor cytological response at 6 months or major (rather than complete) cytogenetic response at 12 months.
Loss of response to tyrosine kinase inhibitors is defined as hematologic relapse, cytogenetic relapse or 1 log increase in \textit{BCR-ABL1} transcript ratio and therefore loss of major molecular response.

Evaluation of \textit{ABL} kinase domain point mutations is \textbf{INVESTIGATIONAL} for monitoring in advance of signs of treatment failure or disease progression.

\textbf{ALL}
\textit{BCR/ABL1} testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR) at baseline prior to initiation of treatment and at appropriate intervals during therapy may be \textbf{MEDICALLY NECESSARY} for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.

Evaluation of \textit{ABL} kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be \textbf{MEDICALLY NECESSARY} when there is inadequate initial response to treatment or any sign of loss of response.

Evaluation of \textit{ABL} kinase domain point mutations is \textbf{INVESTIGATIONAL} for monitoring in advance of signs of treatment failure or disease progression.

\textbf{Medicare HMO Blue}^{\text{SM}} \text{ and Medicare PPO Blue}^{\text{SM}} \text{ Members}

Medical necessity criteria and coding guidance for Medicare Advantage members living in \textit{Massachusetts} can be found through the link below.

\textit{ABL1} (abl proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain (CPT 81170)

\textbf{Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)}

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of \textit{Massachusetts}, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at \url{https://www.cms.gov}.

\textbf{Prior Authorization Information}

\textbf{Inpatient}
- For services described in this policy, precertification/preauthorization \textbf{IS REQUIRED} for all products if the procedure is performed \textit{inpatient}.

\textbf{Outpatient}
- For services described in this policy, see below for products where prior authorization \textbf{might be required} if the procedure is performed \textit{outpatient}.

<table>
<thead>
<tr>
<th>Product</th>
<th>Prior Authorization</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare HMO Blue^{SM}</td>
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</tr>
<tr>
<td>Medicare PPO Blue^{SM}</td>
<td>Prior authorization is not required.</td>
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</tbody>
</table>

\textbf{CPT Codes / HCPCS Codes / ICD Codes}

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.
The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81170</td>
<td>ABL1 (abl proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain</td>
</tr>
<tr>
<td>81206</td>
<td>BCR/ABL1 (t(9;22)) (e.g. chronic myelogenous leukemia) translocation analysis; major breakpoint</td>
</tr>
<tr>
<td>81207</td>
<td>BCR/ABL1 (t(9;22)) (e.g. chronic myelogenous leukemia) translocation analysis; minor breakpoint qualitative or quantitative</td>
</tr>
<tr>
<td>81208</td>
<td>BCR/ABL1 (t(9;22)) (e.g. chronic myelogenous leukemia) translocation analysis; other breakpoint qualitative or quantitative</td>
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</table>

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

### ICD-10-CM Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia not having achieved remission</td>
</tr>
<tr>
<td>C91.01</td>
<td>Acute lymphoblastic leukemia, in remission</td>
</tr>
<tr>
<td>C91.02</td>
<td>Acute lymphoblastic leukemia, in relapse</td>
</tr>
<tr>
<td>C92.10</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission</td>
</tr>
<tr>
<td>C92.11</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in remission</td>
</tr>
<tr>
<td>C92.12</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in relapse</td>
</tr>
</tbody>
</table>

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>0040U</td>
<td>BCR/ABL1 (t(9;22)) (e.g. chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative</td>
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**Description**

In the treatment of Philadelphia chromosome (Ph)-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 point mutations related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

**Background**

*Disease*
CML
Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within 3 to 5 years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, very high or very low platelet counts, etc. From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow.

ALL
Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is the most common childhood tumor, and represents 75% to 80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The median age at diagnosis is 14 years; 60% of patients are diagnosed at younger than 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past several decades, primarily in children, largely due to advances in the understanding of the molecular genetics of the disease, the incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of ~80%. The long-term prognosis among adults is poor, with cure rates of 30% to 40%, explained, in part, by different subtypes among age groups, including the BCR-ABL fusion gene, which has a poor prognosis and is much less common in childhood ALL, as compared with adult ALL.

Disease genetics
Ph-positive leukemias are characterized by the expression of the oncogenic fusion protein product BCR-ABL1, resulting from reciprocal translocation between chromosomes 9 and 22. This abnormal fusion gene characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as BCR-ABL1, are more common. In ALL, the Ph is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is generally associated with acute lymphoblastic leukemia, while p210 is most often seen in CML. The product of BCR-ABL1 is also a functional tyrosine kinase; the kinase domain of the BCR-ABL protein is the same as the kinase domain of the normal ABL protein. However, the abnormal BCR-ABL protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Treatment and response and minimal residual disease
Imatinib (Gleevec®) was originally developed to specifically target and inactivate the ABL tyrosine kinase portion of the BCR-ABL1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in “durable responses in [a] large proportion of the patients with a decreasing rate of relapse.” As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percent of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib. It has been well established that most “good responders” that are considered to be in morphologic remission but relapse may still have considerable levels of leukemia cells, referred to as minimal residual disease (MRD). Among children with ALL who achieve a complete response (CR) by morphologic evaluation after induction therapy, approximately 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD
Detection include flow cytometry (which affords a sensitivity of MRD detection of 0.01%), or polymerase chain reaction (PCR)-based analyses (Ig and T-cell receptor gene rearrangements or analysis of BCR-ABL transcripts), which are the most sensitive method of monitoring treatment response, with a sensitivity of 0.001%. Ig and T-cell receptor gene arrangement analysis is applicable for most ALL patients, whereas PCR analysis of BCR-ABL transcripts is applicable only in Ph-positive patients. With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60% to 80% of patients achieving complete remission, significantly lower than that achieved in Ph-negative ALL. The inclusion of TKIs to frontline induction chemotherapy has improved CR rates, exceeding 90%.

Resistance
Imatinib treatment does not usually result in complete eradication of malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. In addition, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. The molecular basis for resistance is explained in the following section. When the initial response to treatment is inadequate or there is a loss of response, resistance mutation analysis is recommended to support a diagnosis of resistance (based on hematologic or cytogenetic relapse) and to guide the choice of alternative doses or treatments.

Structural studies of the ABL-imatinib complex have resulted in the design of second-generation ABL inhibitors, including dasatinib (Sprycel®) and nilotinib (Tasigna®), which were initially approved by the U.S. Food and Drug Administration (FDA) for treatment of patients resistant or intolerant to prior imatinib therapy. More recently, trials of both agents in newly diagnosed chronic phase patients showed that both are superior to imatinib for all outcomes measured after 1 year of treatment, including CCyR (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis. Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. On June 17, 2010, FDA approved nilotinib for the treatment of patients with newly-diagnosed chronic phase CML. Dasatinib was approved on October 28, 2010, for the same indication.

For patients with increasing levels of BCR-ABL1 transcripts, there is no strong evidence to recommend specific treatment; possibilities include continuation of therapy with dasatinib or nilotinib at the same dose, imatinib dose escalation from 400 mg to 800 mg daily, as tolerated or therapy change to an alternate second-generation TKI are all options.

Molecular resistance
Resistance is most often explained at the molecular level by genomic instability associated with the creation of the abnormal BCR-ABL1 gene, usually resulting in point mutations within the ABL1 gene kinase domain that affects protein kinase-TKI binding. BCR-ABL1 kinase domain (KD) point mutations account for 30% to 50% of secondary resistance. At least 58 different KD mutations have been identified in CML patients. The degree of resistance depends on the position of the mutation within the KD (ie, active site) of the protein. Some mutations are associated with moderate resistance and are responsive to higher doses of TKIs, while other mutations may not be clinically significant. Two mutations, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance. The T315I mutation is relatively common at frequencies ranging from 4% to 19%, depending on the patient population; it is more common in patients with advanced phase CML than in patients with early chronic phase CML.

Compared with imatinib, fewer mutations are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al and Cortes et al studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell BCR-ABL1 mutations. However, neither dasatinib nor nilotinib are effective against resistant clones with the T315I mutation, and new agents and treatment strategies are in development for patients with T315I resistance.
In a recent follow-up study of nilotinib by le Coutre et al, 137 patients with accelerated phase CML were evaluated after 24 months. Sixty-six percent of patients maintained major cytogenetic responses at 24 months. The estimates of overall and progression-free survival rates at 24 months were 70% and 33%, respectively. Grade 3/4 neutropenia and thrombocytopenia were each observed in 42% of patients.

Rarely, other acquired cytogenetic abnormalities such as BCR-ABL gene amplification and protein overexpression have also been reported. Resistance unrelated to kinase activity may result from additional oncogenic activation or loss of tumor suppressor function, and may be accompanied by additional karyotypic changes.

**Summary**

**CML**

Extensive clinical data have led to the development of congruent recommendations and guidelines developed both in North America and in Europe concerning the use of various types of molecular tests relevant to the diagnosis and management of chronic myelogenous leukemia (CML). These tests are also useful in the accelerated and blast phases of this malignancy. Appropriate uses are summarized as follows:

**Diagnosis:** Although CML is diagnosed primarily by clinical and cytogenetic methods, qualitative molecular testing is needed to confirm the presence of the BCR-ABL1 fusion gene, particularly if the Philadelphia chromosome (Ph) was not found, and to identify the type of fusion gene, as this information is necessary for subsequent quantitative testing of fusion gene messenger RNA transcripts. If the fusion gene is not confirmed, then the diagnosis of CML is called into question.

**Monitoring** during treatment with tyrosine kinase inhibitors (TKIs): quantitative determination of BCR-ABL1 transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment. Evaluation of trial samples has consistently shown that the degree of molecular response correlates with risk of progression. In addition, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising BCR-ABL1 transcript levels predict treatment failure and the need to consider a change in management. Quantitative polymerase-chain reaction (PCR)-based methods and international standards (IS) for reporting have been recommended and adopted for treatment monitoring.

**Treatment failure:** the presence of ABL kinase domain point mutations are associated with treatment failure; a large number of mutations have been detected, but extensive analysis of trial data with low-sensitivity mutation detection methods has identified a small number of mutations that are consistently associated with treatment failure with specific TKIs; guidelines recommend testing for, and using information regarding these specific mutations in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography (DHPLC) screening to reduce the number of samples that need to be sequenced. Targeted methods that detect the mutations of interest for management decisions are also acceptable if designed for low sensitivity. High sensitivity assays are not recommended.

While the existing evidence is associational in nature, the body of evidence that has been accumulated and the consequences of the management decisions involved, along with international agreement on recommendations of the use of molecular assays, support the medical necessity of the use of the assays as described. Other uses and other types of assays are considered investigational.

**ALL**

**Diagnosis:** the presence of the BCR-ABL1 fusion gene is not necessary to establish a diagnosis of ALL. However, before initiation of therapy, identification of the BCR-ABL transcript is necessary for risk stratification and quantification to establish baseline levels for subsequent monitoring of response during treatment.

**Monitoring** during treatment with TKIs: quantitative determination of BCR-ABL1 transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment.
Evaluation of trial samples has consistently shown that the degree of molecular response correlates with risk of progression. For ALL, the optimal timing remains unclear and depends upon the chemotherapy regimen used.

Treatment failure: Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL who are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis.

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<tr>
<th>Date</th>
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<tr>
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<td>4/2018</td>
<td>Clarified coding information.</td>
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<td>11/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>4/2016</td>
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<td>1/2016</td>
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<tr>
<td>8/2014</td>
<td>BCBSA National medical policy review.</td>
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<td></td>
<td>New medically necessary and investigational indications described; title changed to include ALL. Coding information clarified. Effective 8/1/2014.</td>
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<tr>
<td>7/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>8/2013</td>
<td>BCBSA National medical policy review.</td>
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<tr>
<td></td>
<td>New policy describing medically necessary and investigational indications. Effective 8/1/2013.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

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
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 or Nilotinib, 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 23873000
