



# Louisiana

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

**Policy #** 00428

**Original Effective Date:** 07/16/2014

**Current Effective Date:** 08/15/2018

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### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

### **Chronic Myelogenous Leukemia**

#### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider *BCR/ABL1* qualitative testing for the presence of the fusion gene for diagnosis of chronic myeloid leukemia (CML) to be **eligible for coverage**.

Based on review of available data, the Company may consider *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription polymerase-chain reaction (RT-PCR) at baseline before initiation of treatment and at appropriate intervals during therapy for monitoring of chronic myeloid leukemia (CML) treatment response and remission to be **eligible for coverage**.

Based on review of available data, the Company may consider evaluation of *ABL* kinase domain single nucleotide variants to assess patients for tyrosine kinase inhibitor (TKI) resistance 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 to be **eligible for coverage**.

#### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers evaluation of *ABL* kinase domain single nucleotide variants for monitoring in advance of signs of treatment failure or disease progression to be **investigational**.\*

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### **Acute Lymphoblastic Leukemia**

#### **When Services Are Eligible for Coverage**

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR) at baseline before initiation of treatment and at appropriate intervals during therapy for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) treatment response and remission to be **eligible for coverage**.

Based on review of available data, the Company may consider evaluation of *ABL* kinase domain single nucleotide variants to assess patients for tyrosine kinase inhibitor (TKI) resistance when there is inadequate initial response to treatment or any sign of loss of response to be **eligible for coverage**.

#### **When Services Are Considered Investigational**

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers evaluation of *ABL* kinase domain single nucleotide variants for monitoring in advance of signs of treatment failure or disease progression to be **investigational**.\*

### **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 CML. Identification of the Philadelphia chromosome is not necessary to diagnose 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.

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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 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. 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.

### **Background/Overview**

#### **MYELOGENOUS LEUKEMIA AND LYMPHOBLASTIC LEUKEMIA**

##### **Chronic Myelogenous Leukemia**

CML is a clonal disorder of myeloid hematopoietic 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, or very high or very low platelet counts. 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.

Extensive clinical data have led to the development of congruent recommendations and guidelines developed both in North America and in Europe on the use of various types of molecular tests relevant to

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the diagnosis and management of CML. These tests are useful in the accelerated and blast phases of this malignancy.

### 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 before 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past, primarily in children, largely due to a better understanding of the molecular genetics of the disease, incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of about 80%. Long-term prognosis among adults is poor, with cure rates of 30% to 40%. Prognosis variation is 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.

### Disease Genetics

Philadelphia (Ph) chromosome–positive leukemias are characterized by the expression of the oncogenic fusion protein product Bcr-Abl1, resulting from a reciprocal translocation between chromosomes 9 and 22. This abnormal fusion product 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 chromosome 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 associated with ALL, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain (KD) of the Bcr-Abl protein is the same as the KD 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.

### 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 Ph chromosome was not found, and to identify the type of fusion gene, because 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.

Determining the qualitative presence of the *BCR-ABL1* fusion gene is not necessary to establish a diagnosis of ALL.

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### **Treatment and Response and Minimal Residual Disease**

Before initiation of therapy for CML or ALL, quantification of the *BCR-ABL* transcript is necessary to establish baseline levels for subsequent quantitative monitoring of response during treatment.

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 the degree of molecular response correlates with risk of progression. Also, 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–based methods and international standards for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec<sup>®</sup>; Novartis, Basel, Switzerland), a TKI, 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.

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 a complete response, significantly lower than that achieved in Ph-negative ALL. The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percentage of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib. It is well established that most “good responders” who 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 by morphologic evaluation after induction therapy, 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (sensitivity of MRD detection, 0.01%), or polymerase chain reaction–based analyses (Ig and T-cell receptor gene rearrangements or analysis of *BCR-ABL* transcripts), which are the most sensitive methods of monitoring treatment response (sensitivity, 0.001%). Most ALL patients can be tested with Ig and T-cell receptor gene arrangement analysis, whereas only Ph-positive patients can be tested with polymerase chain reaction analysis of *BCR-ABL* transcripts.

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### Treatment Resistance

Imatinib treatment does not usually completely eradicate malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. Also, 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 variant 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<sup>®</sup>; Bristol-Myers Squibb, New York, NY) and nilotinib (Tasigna<sup>®</sup>; Novartis, Basel, Switzerland), which were initially approved by the U.S. Food and Drug Administration for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of both agents in newly diagnosed chronic phase patients have shown that both are superior to imatinib for all outcomes measured after 1 year of treatment, including complete cytogenetic response (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. The U.S. FDA has approved third-generation TKIs, ponatinib and bosutinib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI inhibitor is indicated. Bosutinib is indicated for Ph-positive CML with resistance or intolerance to prior therapy.

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, or imatinib dose escalation from 400 to 800 mg daily, as tolerated, or therapy change to an alternative second-generation TKI.

### Molecular Resistance

Molecular resistance is most often explained as genomic instability associated with the creation of the abnormal *BCR-ABL1* gene, usually resulting in point variants within the *ABL1* gene KD that affects protein kinase-TKI binding. *BCR-ABL1* single nucleotide variants (SNVs) account for 30% to 50% of secondary resistance. (Note that new *BCR-ABL* SNVs also occur in 80% to 90% of cases of ALL in relapse after TKI treatment and in CML blast transformation.) At least 58 different SNVs have been identified in CML patients. The degree of resistance depends on the position of the variant within the KD (ie, active site) of the protein. Some variants are associated with moderate resistance and are responsive to higher doses of TKIs, while other variants may not be clinically significant. Two variants, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance.

The presence of *ABL* SNVs is associated with treatment failure. A large number of variants have been detected, but extensive analysis of trial data with low-sensitivity variant detection methods has identified a

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small number of variants consistently associated with treatment failure with specific TKIs; guidelines recommend testing for information on these specific variants to aid in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced. Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.

Unlike imatinib, fewer variants are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al (2007) and Cortes et al (2007) 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* variants. However, neither dasatinib nor nilotinib is effective against resistant clones with the T315I variant. Other treatment strategies are in development for patients with drug resistance.

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. Resistance in ALL to TKIs is less well studied. In patients with ALL receiving a TKI, a rise in the *BCR-ABL* level while in hematologic complete response or clinical relapse warrants variant analysis.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The *BCR-ABL1* fusion gene qualitative and quantitative genotyping tests and *ABL* SNV tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

### **Rationale/Source**

The assessment of a genetic test typically focuses on 3 categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

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### MYELOGENOUS LEUKEMIA AND LYMPHOBLASTIC LEUKEMIA

#### Clinical Context and Test Purpose

Laboratory tests for *BCR-ABL1* detection are associated with CML and Ph chromosome–positive ALL and have different clinical uses. Briefly, they are as follows:

1. Diagnosis: patients who do not have the *BCR-AB1L* fusion gene by definition do not have CML. In contrast, identification of the *BCR-ABL1* fusion gene is necessary, although not sufficient, for diagnosis. Relevant test technologies are cytogenetics (karyotyping; recommended) or fluorescence in situ hybridization (acceptable in the absence of sufficient sample for karyotyping).
2. Monitoring *BCR-ABL1* RNA transcripts for residual disease during treatment or disease remission; relevant, standardized test technology is quantitative RT-PCR. Note that a baseline measurement after confirmation of CML diagnosis and before treatment begins is strongly recommended.
3. Identification and monitoring of variants for drug resistance at response failure or disease progression; various test technologies are in use (not standardized) including RT-PCR and Sanger sequencing.

The question addressed in this evidence review is: Does testing for the *BCR-ABL1* fusion gene improve the net health outcome?

The specific clinical context of each test is described briefly in the following sections. The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is patients with suspected CML (to confirm the diagnosis) or patients with diagnosed CML or Ph chromosome–positive ALL.

#### **Interventions**

The interventions of interest are various tests that assess the presence of the *BCR-ABL1* fusion gene, monitor transcript levels, and identify variants.

#### **Comparator**

The comparator of interest is standard workup with cytogenetics.

#### **Outcomes**

The outcomes of interest are the analytic and clinical validity for the detection of the *BCR-ABL1* fusion gene, transcript levels, and variants. Testing to monitor treatment response and detection of variants in *BCR-ABL1* will impact the selection of tyrosine kinase medications and affect disease progression.

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### **Timing**

The time of interest is before diagnosis, during treatment for monitoring, and when patients show treatment resistance.

### **Setting**

These tests are offered through a variety of commercial and noncommercial laboratories.

### **Chronic Myelogenous Leukemia**

#### ***Diagnosis and Pretreatment Workup***

While the diagnosis of CML is based on the presence of characteristic cellular abnormalities in bone marrow, the presence of the Ph chromosome and/or confirmation of the *BCR-ABL1* fusion gene is essential. The initial evaluation of chronic phase CML should include bone marrow cytogenetics, not only to detect the Ph chromosome, but also to detect other possible chromosomal abnormalities. If bone marrow is not available, fluorescence in situ hybridization analysis with dual probes for *BCR* and *ABL* genes or qualitative RT-PCR can provide qualitative confirmation of the fusion gene and its type.

#### *Section Summary: Diagnosis and Pretreatment Workup*

The evidence on diagnosis and pretreatment workup in patients with CML includes validation studies. The sensitivity of testing *BCR-ABL* transcript levels with rt-PCR is high compared with conventional cytogenetics. Baseline measurement of *BCR-ABL* transcript levels is recommended as part of the initial evaluation, confirming the fusion gene, ensuring that it is detectable (rare variants requiring nonstandard probes may occur), and providing a baseline for monitoring response to treatment.

#### ***Monitoring for Residual Disease During Treatment and Disease Remission***

Quantitative RT-PCR (qRT-PCR) measurement of *BCR-ABL1* RNA transcript levels is the method of choice for assessing response to treatment because of the high sensitivity of the method and strong correlation with outcomes. Compared with conventional cytogenetics, qRT-PCR is more than 3 logs more sensitive and can detect 1 CML cell in the background of 100,000 or more normal cells. Quantitative RT-PCR testing can be conducted on peripheral blood, eliminating the need for bone marrow sampling. The goal of treatment is complete molecular response (CMR; no detectable *BCR-ABL* transcript levels by qRT-PCR). However, only a small minority of patients achieve CMR on imatinib. More often, patients achieve a major molecular response (MMR; a 3-log reduction from the standardized baseline of the International Scale (IS; not from the actual baseline level of the individual patient). Results from the 2006 IRIS trial showed that patients who had a CMR or MMR had a negligible risk of disease progression at 1 year, and a significantly lower risk of disease progression at 5 years than patients who had neither. At 8-year follow-up, none of the patients who achieved an MMR at 1 year progressed to the accelerated phase of disease or to a blast crisis. Similar near absence of progression in patients who achieved an MMR has been reported in registration studies of nilotinib and dasatinib.

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The degree of molecular response has been reported to correlate with risk of progression in patients treated with imatinib. Timing of the molecular response is also important; the degree of molecular response at early time points predicts the likelihood of achieving CMR or MMR and predicts improved rates of progression-free and event-free survival. While early and strong molecular response predicts durable long-term remission rates and progression-free survival, studies have not been conclusive that molecular response is predictive of overall survival.

Based on imatinib follow-up data, it is recommended that, for patients with a complete cytogenetic response (CCyR), molecular response to treatment be measured every 3 months for 2 years, then every 3 to 6 months thereafter. Without 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.

Rising *BCR-ABL1* transcript levels are associated with increased risk of variants and of treatment failure. However, what constitutes a clinically significant rise to warrant variant testing is not known. Factors affecting the clinically significant change include the variability of the specific assay used by the laboratory and the level of molecular response achieved by the patient. Thresholds used include 2- to 10-fold increases, and increases of 0.5 to 1 log, respectively. Because of potential variability in results and lack of agreement across studies for an acceptable threshold, rising transcript levels alone are not viewed as sufficient to trigger variant testing or changes in treatment.

### *Standardization of BCR-ABL1 Quantitative Transcript Testing*

A substantial effort has been made to standardize the *BCR-ABL1* qRT-PCR testing and reporting across academic and private laboratories. In 2006, the National Institute of Health Consensus Group proposed an IS for *BCR-ABL1* measurement. The IS defines 100% as the median pretreatment baseline level of *BCR-ABL1* RNA in early chronic phase CML; as determined in the pivotal IRIS trial, MMR is defined as a 3-log reduction relative to the standardized baseline, or 0.1% *BCR-ABL1* on the IS. In the assay, *BCR-ABL1* transcripts are quantified relative to 1 of 3 recommended reference genes (eg, *ABL*) to control for the quality and quantity of RNA and to normalize for potential differences between tests. Percent ratios on the IS are determined at local labs by a test-specific conversion factor:

IS percent ratio = local percent ratio × conversion factor.

Until reference standards become broadly available, patient specimens must be exchanged between the local laboratory and an IS reference laboratory to establish a laboratory-specific conversion factor. In the United States, many laboratories offer *BCR-ABL* quantitative testing (eg, Quest, ARUP, LabCorp, Mayo), and most specify on their websites that results are standardized to the IS.

### *Section Summary: Monitoring for Residual Disease During Treatment and Disease Remission*

The evidence on monitoring for residual disease during treatment and disease remission in patients with CML includes a randomized controlled trial and case series. Quantitative RT-PCR (qRT-PCR)

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measurement of *BCR-ABL1* RNA transcript levels is the method of choice for assessing response to treatment in CML because of the high sensitivity, strong correlation with outcomes, and ability to sample in peripheral blood.

### Identification of *ABL* Kinase Domain Single Nucleotide Variants to Assess TKI Resistance

Screening for *BCR-ABL1* KD SNVs in chronic phase CML is recommended for patients with (1) inadequate initial response to TKI treatment, (2) evidence of loss of response, or (3) progression to accelerated or blast phase CML. Testing for KD SNVs, in the setting of potential treatment failure, may help to select from among other TKI treatments or allogeneic cell transplantation. The following discussion focuses only on KD SNVs.

In 2010, the Agency for Healthcare Research and Quality published a systematic review on *BCR-ABL1* pharmacogenetic testing for TKIs in CML. The report concluded that the presence of any *BCR-ABL1* variant does not predict differential response to TKI therapy, although the presence of the T315I variant uniformly predicts TKI failure. The review was strongly criticized by respected pathology organizations for insufficient attention to several issues. Importantly, the report grouped studies that used KD SNV screening methods with those that used targeted methods, and grouped studies that used variant detection technologies with very different sensitivities. The report discounted issues related to analytic validity. However, in this clinical scenario, assays used for different reasons (screening vs targeted) and assays with very different sensitivities may lead to different clinical conclusions.

### *SNV Detection Methods*

Currently, methods for detecting drug resistance variants are not standardized; clinical laboratories may choose among different methods. Some can detect specific, known variants (eg, targeted variant analysis) or screen for all possible variants (eg, direct sequencing); sensitivity also varies by method.

Particular methods to detect *BCR-ABL* KD SNVs will greatly influence the detection frequency, analytic sensitivity, and clinical impact of testing. The various variant detection methods available have widely differing analytic sensitivities, from the least sensitive direct Sanger sequencing to the highly sensitive variant-specific quantitative polymerase chain reaction methods.

Direct Sanger sequencing screens for all possible variants but has low sensitivity, detecting a variant present in approximately 1 in 5 *BCR-ABL1* transcripts. Denaturing high-performance liquid chromatography is a screening method with initially higher sensitivity to detect the presence or absence of variants. Follow-up Sanger sequencing of positive samples is required to identify the variants present; the final sensitivity of this method is the sensitivity of sequencing. Targeted methods, used either to screen for only the most common, clinically relevant variants or to monitor already identified variants after a therapy change, can offer either limited sensitivity (eg, pyrosequencing) or very high sensitivity (eg, allele-specific polymerase chain reaction). Next-generation sequencing has also been proposed to detect *BCR-ABL1* variants relevant to TKI choice in imatinib-resistant patients.

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# Louisiana

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

Policy # 00428

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### *KD SNVs and Treatment Outcomes*

Branford et al summarized the available evidence in 2009 on KD SNVs detected at imatinib treatment failure, and subsequent treatment success or failure with dasatinib or nilotinib. Studies referenced used direct Sanger sequencing, with or without denaturing high-performance liquid chromatography screening, to identify variants at low sensitivity. The authors surveyed variants detected in patients at imatinib failure at their own institution and compared results with a collation of variants derived from the literature. For both, the T315I variant was most common; although about 100 variants have been reported, the 7 most common (at residues T315, Y253, E255, M351, G250, F359, and H396) accounted for 60% to 66% of all variants in both surveys. Detection of the T315I variant at imatinib failure is associated with lack of subsequent response to high-dose imatinib or to dasatinib or nilotinib. For these patients, allogeneic cell transplantation was the only available treatment until the approval of new agents (eg, ponatinib). Most common, however, does not necessarily correspond to clinically significant. Based on the available clinical studies, most imatinib-resistant variants remain sensitive to dasatinib and nilotinib. However, preexisting or emerging variants T315A, F317L, F317I, F317V, F317C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging variants Y253H, E255K, E255V, and F359V, and F359C have been reported to have decreased clinical efficacy with nilotinib treatment following imatinib failure. In the Branford survey, 42% of patients tested had T315I or one of the dasatinib- or nilotinib-resistant variants. As a result, guidelines recommend variant analysis only at treatment failure, and use of the T315I variant and the identified dasatinib- and nilotinib-resistant variants to select subsequent treatment. Absent any of these actionable variants, various treatment options are available. Note that these data were obtained from studies of patients all initially treated with imatinib.

ABL KD SNV analysis is recommended if there is inadequate initial response (failure to achieve complete hematologic response at 3 months, only minor cytologic response at 6 months, or major [rather than complete] cytogenetic response at 12 months) or any sign of loss of response (defined as hematologic relapse, cytogenetic relapse, or 1-log increase in *BCR-ABL1* transcript ratio and therefore loss of MMR). Variant testing is also recommended for progression to accelerated or blast phase CML. Treatment recommendations based on variant(s) are shown in Table 1.

Because only a small number of variants have been recommended as clinically actionable, targeted assays may also be used to screen for the presence of actionable variants at treatment failure. Quantitative, targeted assays may also be used to monitor levels of already identified clinically significant variants after starting a new therapy because of initial treatment failure. Targeted assays use different technologies that can be very sensitive and pick up mutated cell clones at very low frequencies in the overall malignant population. Banked samples from completed trials have been studied with high-sensitivity assays to determine if monitoring treatment can detect low-level variants that predict treatment failure well in advance of clinical indications. Some results have been positive, but not all variants detected in advance predict treatment failure; more study is recommended before these assays are used for monitoring in advance of treatment failure. A direct correlation between low-sensitivity and high-sensitivity assays and a limited correlation with clinical outcomes support recommendations of sequencing, with or without denaturing high-

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performance liquid chromatography screening, for identification of variants. Although high-sensitivity assays identified more variants than did sequencing, the clinical impact of identifying additional variants is uncertain.

Variants other than point variants can be detected in the *BCR-ABL1* gene, including alternate splicing, insertions, deletions, and/or duplications. The clinical significance of such altered transcripts is unclear, and reporting such variants is not recommended.

### **Section Summary: Identification of ABL KD SNVs to Assess TKI Resistance**

The evidence on identification of *ABL* SNVs to assess TKI resistance in patients with CML includes a systematic review and case series. These studies have evaluated pharmacogenetics testing for tyrosine kinase inhibitors and have shown a correlation between certain types of variants and treatment response. Testing for SNVs, in the setting of potential treatment failure, may help to select from among other TKI treatments or allogeneic cell transplantation.

### **Acute Lymphoblastic Leukemia**

#### **Diagnosis and Pretreatment Workup**

The diagnosis of ALL is made by demonstrating 20% or greater bone marrow lymphoblasts; demonstration of the *BCR-ABL* fusion gene is not essential. However, identification of specific molecular subtypes is recommended at the time of diagnosis for optimal risk evaluation and treatment planning. The initial evaluation of ALL patients should include bone marrow sample for RT-PCR for *BCR-ABL* to establish the presence or absence of *BCR-ABL*, as well as baseline transcript quantification.

#### **Monitoring for Residual Disease During Treatment and Disease Remission**

Despite significantly higher complete response rates with TKIs in Ph-positive ALL, the response is typically short-lived, and relapses are common. The principal aim of after remission therapy is to eradicate minimal residual disease (MRD), which is the prime cause of relapse.

Studies in children and adults with ALL have demonstrated a strong correlation between MRD and risk for relapse, as well as the prognostic significance of measuring MRD during and after initial induction therapy. A commonly used cutoff to define MRD positivity is 0.01%, with patients who attain an MRD less than 0.01% early during therapy having high odds of remaining in continuous complete response with contemporary postremission therapy.

A study of 3184 B-cell ALL children enrolled in the AIEOP-BFM ALL 2000 treatment protocol demonstrated that a risk classification algorithm based on MRD measurements using polymerase chain reaction on days 33 and 78 of treatment was superior to that of other risk stratification criteria based on white blood cell count, age, early response to prednisone, and genetic subtype. Patients with an MRD less than 0.01% on day 33 (42%) had a 5-year event-free survival of 92.3%.

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MRD is also a strong prognostic factor for children and adolescents with first-relapse ALL who achieve a second remission. Patients with an MRD of 0.01% or more are eligible for allogeneic hematopoietic cell transplantation, whereas achievement of MRD negativity may be an indication for chemotherapy.

*Section Summary: Diagnosis, Pretreatment Workup, and Monitoring for Residual Disease During Treatment and Disease Remission*

Evidence on the diagnosis, pretreatment workup, and monitoring for residual disease during treatment and disease progression in patients with Ph chromosome–positive ALL includes a prospective cohort study and case series. These studies have shown a high sensitivity for *BCR-ABL1* quantitative testing and a strong correlation with outcomes, including the risk of disease progression. This may stratify patients to different treatment options.

### **Identification of ABL KD SNVs Associated With TKI Resistance**

Resistance to TKIs in ALL is less well studied. Detection of variants was used to evaluate insensitivity to second- or third-generation TKI in case series (2016). Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or competition of other coexisting subclones. In patients with ALL receiving a TKI, a rise in the Bcr-Abl protein level while in hematologic complete response or clinical relapse warrants variant analysis.

*Section Summary: Identification of ABL SNVs Associated With TKI Resistance*

Evidence on the identification of *ABL* SNVs associated with TKI resistance in patients with Ph chromosome–positive ALL includes case series. These studies have shown that specific imatinib-resistant variants are insensitive to one or both of the second-generation tyrosine kinase inhibitors. These variants are used to guide medication selection.

## **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.

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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.

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- 07/10/2014 Medical Policy Committee review
  - 07/16/2014 Medical Policy Implementation Committee approval. New policy.
  - 08/06/2015 Medical Policy Committee review
  - 08/19/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 08/04/2016 Medical Policy Committee review
  - 08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
  - 08/03/2017 Medical Policy Committee review
  - 08/23/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 04/01/2018 Coding update
  - 08/09/2018 Medical Policy Committee review
  - 08/15/2018 Medical Policy Implementation Committee approval. Added policy guidelines.
- Next Scheduled Review Date: 08/2019

### Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0016U, 81170, 81206, 81207, 81208, 81401, 81403 Code added eff 4/1/18: 0040U
HCPCS	No codes
ICD-10 Diagnosis	C91.00 C91.01 C91.02 C92.10 C92.11 C92.12

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

\*\*Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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# Louisiana

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

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For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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