BlueCross BlueShield of Alabama

## Name of Policy:

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

Policy #: 533
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: B

## Background/Definitions:

*As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.*

*The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:*

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

*Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:*

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

## Description of Procedure or Service:

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 (TKIs), or disease progression.

**Myelogenous Leukemia and Lymphoblastic Leukemia**

Chronic Myelogenous Leukemia (CML)

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 three to five years to the accelerated phase, characterized by any of several specific criteria such as 10-19% 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 the diagnosis and management of CML. These tests are also useful in the accelerated and blast phases of this malignancy.

Acute Lymphoblastic Leukemia

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 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 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.

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 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.

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. 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 for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec®; Novartis, Basel, Switzerland), a tyrosine kinase inhibitor (TKI), was originally developed to specifically target and inactivate the *ABL* tyrosine kinase portion of the *BCR-ABL1* fusion protein in order to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared to 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 (CR), 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 (percent of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by six to 12 months after initial treatment with the TKI imatinib. It has been 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 or 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 (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 methods of monitoring treatment response, (sensitivity of 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.

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. 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 variant analysis is recommended to support a diagnosis of resistance (based on hematologic or cytogenetic relapse), and 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. Trials of both agents in newly diagnosed chronic phase patients showed that both are superior to imatinib for all outcomes measured after one 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. The U.S. Food and Drug Administration 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 mg to 800 mg daily, as tolerated or therapy change to an alternate 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 (i.e., 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 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 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.

## Policy:

### CML

***BCR-ABL1* qualitative testing** for the presence of the fusion gene **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for diagnosis of chronic myeloid leukemia** (see Policy Guidelines).

***BCR-ABL1* testing** for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction **meets** Blue Cross and Blue Shield of Alabama's medical

criteria for coverage **for monitoring of chronic myeloid leukemia treatment response and remission at:**

- Baseline prior to initiation of treatment; **and**
- At appropriate intervals (see Policy Guidelines).

**Evaluation of *ABL* kinase domain single nucleotide variants meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **to assess patients for tyrosine kinase inhibitor resistance** for **any** of the following indications:

- There is an inadequate initial response to treatment; **or**
- Any sign of loss of response

**Evaluation of *ABL* kinase domain single nucleotide variants does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for monitoring in advance of signs of treatment failure or disease progression** and is considered **investigational.**

**ALL**

***BCR-ABL1* testing** for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission at:**

- Baseline prior to initiation of treatment; **and**
- At appropriate intervals during therapy (see Policy Guidelines).

**Evaluation of *ABL* kinase domain single nucleotide variants meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **to assess patients for tyrosine kinase inhibitor resistance** for the following indication:

- There is an inadequate initial response to treatment; **or**
- Any sign of loss of response.

**Evaluation of *ABL* kinase domain single nucleotide variants does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for monitoring in advance of signs of treatment failure or disease progression** and is considered **investigational.**

## Policy Guidelines:

**Diagnosis of CML and ALL**

Qualitative molecular confirmation of the cytogenetic diagnosis (i.e., detection of the Philadelphia chromosome) is necessary information for the accurate diagnosis of CML. Identification of the Philadelphia chromosome is not necessary for the diagnosis of ALL, however, molecular phenotyping is usually performed at the time of initial assessment (See Determining Baseline RNA Transcript Levels and Subsequent Monitoring).

Distinction between molecular variants (i.e., p190 vs. p210) is necessary information for accurate diagnosis and 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.
- 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 during treatment.

Without a complete cytogenetic response, continued monitoring at three-month intervals during treatment is recommended.

There is the assumption that the same time points for the monitoring of imatinib are also appropriate for dasatinib and nilotinib and will likely also be applied to bosutinib and ponatinib.

More frequent monitoring is indicated for patient diagnosed with **CML** who are in complete molecular remission and are not undergoing treatment with a TKI.

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

**TKI Resistance**
For **CML**, 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.

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 variant analysis.

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

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.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical*

*judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## Key Points:

This policy has been updated with a MEDLINE literature search through August 22, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Laboratory tests for *BCR-ABL1* detection are associated with chronic myelogenous leukemia (CML) and Philadelphia (Ph) chromosome-positive acute lymphoblastic leukemia (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 (FISH; acceptable in the absence of sufficient sample for karyotyping).
2. Monitoring *BCR-ABL1* RNA transcripts for residual disease during treatment/disease remission; relevant, standardized test technology is quantitative reverse transcription-polymerase chain reaction (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/disease progression; various test technologies are in use (not standardized) including RT-PCR and Sanger sequencing.

### Chronic Myelogenous Leukemia Diagnosis and Pretreatment Workup

Clinical Context and Test Purpose

The purpose of BCR-ABL1 fusion gene qualitative testing in individuals with suspected chronic myelogenous leukemia (CML) is to inform diagnosis and establish baseline for monitoring treatment.

The question addressed in this evidence review is: Does qualitative testing of BCR-ABL1 improves the net health outcome in individuals with CML or Ph-positive ALL?

The following PICOTS were used to select literature to inform this review.

*Patients*
The relevant population of interest is individuals with suspected CML.

*Interventions*
The therapy being considered is BCR-ABL1 fusion gene qualitative testing.

*Comparators*
The following practices are currently being used to diagnose CML and or Ph-positive ALL: clinical and cytogenetic methods.

*Outcomes*
The general outcome of interest is test validity.

*Timing*
Follow-up over years is of interest for demonstrating test accuracy and test validity.

*Setting*
Patients with suspected CML are actively managed by hematologists and oncologists in an outpatient clinical setting.

Study Selection Criteria
For the evaluation of clinical validity of the BCR-ABL1 fusion gene qualitative testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Validation Studies
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 Treatment Response and Disease Remission**

Clinical Context and Test Purpose

The purpose of BCR-ABL1 quantitative testing at appropriate intervals in patients with a diagnosis of CML is to monitor treatment response and remission.

The question addressed in this evidence review is: Does quantitative testing of BCR-ABL1 improve health outcomes in individuals with CML?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with a diagnosis of CML.

Interventions

The therapy being considered is BCR-ABL1 quantitative testing at appropriate intervals.

Comparators

The following practice is currently being used to diagnose CML: cytogenetics.

Outcomes

The general outcomes of interest are disease-specific survival, test validity, and change in disease status.

Timing

Follow-up over years is of interest for disease-specific survival, test validity, and change in disease status.

Setting

Patients with a diagnosis of CML are actively managed by hematologists and oncologists in an outpatient clinical setting.

**Study Selection Criteria**

For the evaluation of clinical validity of the BCR-ABL1 qualitative testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

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), which has variable definitions based on the assay; 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), which may be defined as BCR-ABL1 (International Scale) ≤ 0.1% or a ≥ 3-log reduction in BCRABL1 mRNA 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.

Several studies have used these tests to guide discontinuation of select TKIs in CML patients who have achieved an appropriate molecular response, and to monitor treatment-free remission. The largest of these studies, the EURO-SKI trial (2018), evaluated discontinuation of TKIs in patients with CML who had been treated with TKIs for more than 3 years and had achieved MR4 (Molecular Response; ≤0.01% BCRABL1 IS) for at least 1 year (N=755). Molecular response was assessed monthly for the first 6 months, every 6 weeks for the remainder of the year, and then every 3 months for at least 3 years. The trigger to resume treatment with TKIs was loss of MMR. Treatment-free remission rate was 50% at 2 years (95% CI 46-54); loss of MMR despite restarting TKIs was seen in 2 patients. Similar findings were seen in recent updates of the ENESTfreedom Study (2018), a large single-arm phase 2 study, which evaluated discontinuation of first-line treatment with nilotinib in patients with CML who had been treated with nilotinib for more than 2 years and achieved sustained deep molecular response (N=190). Molecular response was assessed monthly for the next 48 weeks, every 6 weeks for the next 48 weeks, and then every 3 months for the time remaining. The trigger to resume treatment with TKIs was loss of MMR. Treatmentfree remission rate was 49% at 96 weeks (95% CI, 42% to 56%); loss of MMR despite restarting TKIs was seen in 1 patient. Adverse events including musculoskeletal pain were noted in both the EURO-SKI and ENESTfreedom Study; no progression to CML accelerated phase or blast crisis was noted.

The degree of molecular response has also 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 three months for two years, then every three to six months thereafter. Without complete cytogenetic response (CCyR), continued monitoring at three-month intervals is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib as well, 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, as well as the level of molecular response achieved by the patient. Thresholds used include two- to ten-fold increases, and increases of 0.5 to one 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 International Scale (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 three-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 one of three recommended reference genes (e.g., *ABL*) to control for the quality and quantity of RNA and to normalize for potential differences between tests.

Section Summary: 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 monitoring CML during treatment and in disease remission 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**

Clinical Context and Test Purpose

The purpose of the evaluation for ABL kinase domain (KD) single nucleotide variants (SNVs) in patients with a diagnosis of CML with inadequate initial response, loss of response, and/or disease progression is to assess for TKI resistance.

The question addressed in this evidence review is: Does evaluation for ABL KD SNVs s improve health outcomes in individuals with CML with inadequate initial response, loss of response, and/or disease progression?

The following PICOTS were used to select literature to inform this review.

*Patients*

The relevant population of interest is individuals with a diagnosis of CML with inadequate initial response, loss of response, and/or disease progression.

*Interventions*

The therapy being considered is an evaluation for ABL KD SNVs to assess for TKI resistance.

*Comparators*

The following practice is currently being used to diagnose CML in those with inadequate initial response, loss of response, and/or disease progression: standard workup without genetic testing.

*Outcomes*
The general outcomes of interest are disease-specific survival, test validity, and medication use.

*Timing*
Follow-up over years is of interest for disease-specific survival, test validity, and medication use.

*Setting*
Patients are actively managed by hematologists and oncologists in an outpatient clinical setting.

Study Selection Criteria
For the evaluation of clinical validity of the ABL KD SNV testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Screening for *BCR-ABL1* kinase domain (KD) single-nucleotide variants (SNVs) in chronic phase CML is recommended for patients with (1) inadequate initial response to tyrosine kinase inhibitor (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 (e.g., targeted variant analysis) or screen for all possible variants (e.g., 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 (e.g., pyrosequencing) or very high sensitivity (e.g., 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.

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 seven 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 (e.g., 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 three 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-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**
Clinical Context and Test Purpose
The purpose of BCR-ABL1 quantitative testing at baseline before and during treatment in patients with a diagnosis of Ph-positive ALL is to monitor treatment response and remission.

The question addressed in this evidence review is: Does quantitative testing of BCR-ABL1 improve health outcomes in individuals with Ph-positive ALL?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with a diagnosis of Ph-positive ALL.

Interventions
The therapy being considered is BCR-ABL1 quantitative testing at baseline before and during treatment to monitor treatment response and remission.

Comparators
The following test is currently being used to monitor treatment response and remission in those diagnosed with Ph-positive ALL: cytogenetics.

Outcomes
The general outcomes of interest are disease-specific survival, test validity, and change in disease status.

Timing
Follow-up over years is of interest for disease-specific survival, test validity, and change in disease status.

Setting
Patients are actively managed by hematologist/oncologists in an outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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 MRD less than 0.01% early during therapy having high odds of remaining in continuous complete remission with contemporary postremission therapy.

A study of 3184 B-cell acute lymphoblastic leukemia (ALL) children enrolled in the AIEOP-BFM ALL 2000 treatment protocol demonstrated that a risk classification algorithm based on

MRD measurements using PCR 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 MRD less than 0.01% on day 33 (42%) had a 5-year event free survival of 92.3%.

MRD is also a strong prognostic factor for children and adolescents with first-relapse ALL who achieve a second remission. Patients with 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**

Clinical Context and Test Purpose

The purpose of evaluation for ABL KD SNVs in patients with Ph-positive ALL and signs of treatment failure or disease progression is to assess for TKI resistance.

The question addressed in this evidence review is: Does testing of ABL KD SNVs improves health outcomes in individuals with Ph-positive ALL?

The following PICOTS were used to select literature to inform this review.

*Patients*

The relevant population of interest is individuals with Ph-positive ALL and signs of treatment failure or disease progression.

*Interventions*

The therapy being considered is an evaluation for ABL KD SNVs to assess for TKI resistance.

*Comparators*

The following practice is currently being used to monitor patients with Ph-positive ALL and signs of treatment failure or disease progression: standard workup without genetic testing.

*Outcomes*

The general outcomes of interest are test validity and medication use.

*Timing*

Follow-up over years is of interest for test validity and medication use.

*Setting*
Patients with are actively managed by hematologist/oncologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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 outcome is 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 for monitoring treatment response and remission, the evidence includes a randomized trial and case series. Relevant outcomes are disease-specific survival, test 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 options for disease management. 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 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 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 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.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) Practice Guidelines v.1.2019 on Chronic Myelogenous Leukemia outline recommend methods for diagnosis and treatment management of CML, including *BCR-ABL1* tests for diagnosis, monitoring, and *ABL* kinase domain single nucleotide variants (see Table 1). Guidelines for discontinuation of tyrosine kinase inhibitor therapy are detailed; molecular monitoring is recommended every month for 1 year, every 6 weeks for the second year, and every 12 weeks afterward.

**Table 1. Treatment Options Based on BCR-ABL1 Variant Profile**

| Single Nucleotide Variants | Treatment Recommendation |
|---|---|
| T315I | Ponatinib, omacetaxine, allogeneic HCT, or clinical trial |
| V299L, T315A, F317L, F317V, F317I, F317C | Nilotinib |
| Y253H, E255K, E255V, F359V, F359C, F359I | Dasatinib |
| E255K, E255V, F317L, F317V, F317I, F317C, F359V, F359C, F359I, T315A, Y253H | Bosutinib |

HCT: hematopoietic cell transplantation

The NCCN Practice Guidelines (v.1.2018 ) on Acute Lymphoblastic Leukemia (ALL) state that, if MRD is being evaluated, the initial measurement should be performed on completion of initial 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 over the course of sequential therapy. 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 Options Based on BCR-ABL1 Variant Profile**

| Single Nucleotide Variants | Treatment Recommendation |
|---|---|
| T315I | Ponatinib |
| V299L, T315A, F317L, F317V, F317I, F317C | Nilotinib |
| Y253H, E255K, E255V, F359V, F359C, F359I | Dasatinib |
| E255K, E255V, F317L, F317V, F317I, F317C, F359V, F359C, F359I, T315A, Y253H | Bosutinib |

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.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

## Key Words:

BCR-ABL1 genotyping, chronic myeloid leukemia, CML, BCR-ABL1 mRNA quantification, ABL kinase domain mutation testing, genetic testing, acute lymphoblastic leukemia, ALL, fusion gene, imatinib, Gleevac, dasatinib, Sprycel, nilotinib, Tasigna, bosutinib, ponatinib, ABL kinase domain single nucleotide variants, BCR-ABL1, TKI, tyrosine kinase inhibitor

## Approved by Governing Bodies:

On July 2016, QuantideX® qPCR BCR-ABL IS Kit (Asuragen) was approved by FDA through the de novo 510(k) pathway (DEN160003). This test may be used in patients with diagnosed t(9;22) positive CML, during treatment with TKIs, to measure BCR-ABL mRNA transcript levels. It is not intended for use in diagnosing CML. FDA classification code: OYX.

On December 2017, the MRDx® BCR-ABL Test (MolecularMD) was approved by FDA through the 510(k) pathway (K173492). The test may be used in patients with diagnosed t(9;22) positive CML, during treatment with TKIs, to measure BCR-ABL mRNA transcript levels. It is also intended for use "in the serial monitoring for BCR-ABL mRNA transcript levels as an aid in identifying CML patients in the chronic phase being treated with nilotinib who may be candidates for treatment discontinuation and for monitoring of treatment-free remission." FDA classification code: OYX.

Additionally, 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. Food and Drug Administration has chosen not to require any regulatory review of this test.

## Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved. Review will be performed for medical necessity.

## Current Coding:

CPT Codes:

| | |
|---|---|
| **81170** | ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain |
| **81206** | BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative |
| **81207** | BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative |
| **81208** | BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative |
| **0016U** | Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation. |
| **0040U** | BCR/ABL1 (t(9:22)) (e.g. chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative **(Effective 04/01/2018)** |

Testing for *ABL* kinase domain point mutations to evaluate patients for TKI resistance would be reported with the following codes:

| | |
|---|---|
| **81401** | Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) – Includes *ABL1 (ABL proto-oncogene 1,non-receptor tyrosine kinase)* (e.g., acquired imatinib resistance), T315I variant |

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## Policy History:

Medical Policy Group, March 2011 **(1)** BCR-ABL1 mutation analysis for management of CML is considered investigational as of 3/22/2010 (originally contained in medical policy #133)
Medical Policy Administration Committee, March 2011
Available for comment April 4 – May 18, 2011
Medical Policy Panel, February 2013
Medical Policy Group, July 2013 **(1):** Creation of individual policy with all references related to BCR-ABL1 removed from medical policy #133; change in criteria to cover BCR-ABL1 mutation analysis for dx, monitoring and managing treatment of CML with change to become effective 01/01/2013; all corresponding tables and informational pages have been updated
Medical Policy Administration Committee, August 2013
Available for comment July 26 through September 15, 2013
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 **(1):** Update to Title, Description, Policy, Key Points, Key Words, Coding and References related to addition of new coverage criteria for disease monitoring and evaluating for TKI resistance for ALL
Medical Policy Administration Committee, April 2014
Available for comment April 10 through May 24, 2014
Medical Policy Panel, March 2015
Medical Policy Group, March 2015 **(3):** Updates to Key Points; no change in policy statement.
Medical Policy Group, November 2015: 2016 Annual Coding Update; Added new CPT code 81170 to current coding. Moved CPT code 81403 from current coding to previous coding
Medical Policy Panel, March 2016

Medical Policy Group, March 2016 **(3)**: 2016 Updates to Description, Key Points, Coding & References; no change in policy statement
Medical Policy Group, July 2017: Ad hoc coding update. Added CPT code 0016U to current coding.
Medical Policy Panel, October 2017
Medical Policy Group, November 2017 **(3):** 2017 Updates to Description, Key Points, Approved by Governing Bodies & References. Removed policy statements for dates January 1, 2013 – February 28, 2014 and dates prior to January 1, 2013. Edited current policy section; no change in policy statement; removed previous coding section for coding deleted 1/1/13.
Medical Policy Group, March 2018. Quarterly Coding Update, April 2018. Added new CPT code 0040U to Current Coding.
Medical Policy Panel, October 2018
Medical Policy Group, October 2018 **(9)**: 2018 Updates to Description, Key Points, Policy Guidelines, Policy Statement (added clarifying wording "for the presence of the fusion gene"; no change to policy intent), Approved by Governing Bodies & References. Added key words: fusion gene, imatinib, Gleevac, dasatinib, Sprycel, nilotinib, Tasigna, bosutinib, ponatinib, ABL kinase domain single nucleotide variants, BCR-ABL1, TKI, tyrosine kinase inhibitor

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