I. POLICY

Chronic Myeloid Leukemia (CML)

BCR/ABL1 qualitative testing for the presence of the fusion gene is considered medically necessary 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 at baseline prior to initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines) is considered medically necessary for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of ABL kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance is considered medically necessary when there is inadequate initial response to treatment or any sign of loss of response (see Policy Guidelines); and/or when there is progression of the disease to the accelerated or blast phase.

Evaluation of ABL kinase domain point mutations is considered investigational for monitoring in advance of signs of treatment failure or disease progression. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Acute Lymphoblastic Leukemia (ALL)

BCR/ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR) at baseline prior to initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines section) is considered medically necessary for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.
Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance is considered **medically necessary** when there is inadequate initial response to treatment or any sign of loss of response.

Evaluation of *ABL* kinase domain point mutations is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

**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 generally performed at the time of initial assessment (see Determining Baseline RNA Transcript Levels and Subsequent Monitoring subsection).

Distinction between molecular variants (i.e., *p*190 vs *p*210) is necessary information 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 RT-PCR-based assays, and reported results should be standardized according to the International Scale.

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

Without attainment of 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 as well and will likely also be applied to bosutinib and ponatinib (see Rationale section for more information).

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

**Tyrosine Kinase Inhibitor Resistance**

For CML, inadequate initial response to TKIs is defined as 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.
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 \( BCR-ABL \) mRNA level while in hematologic CR or clinical relapse warrants mutational 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 (MMR).

Kinase domain mutation testing is usually offered either as a single test to identify T315I mutation or as a panel (which includes T315I) of the most common and clinically important mutations.

**Cross-reference:**
MP-2.174 Omacetaxine Mepesuccinate (Synribo®)

### II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*        BlueJourney PPO*        FEP PPO**

*Refer to Novitas Solutions Local Coverage Determination (LCD) 35396 Biomarkers for Oncology.

** Refer to FEP Medical Policy Manual MP-2.04.85, BCR-ABL 1 Testing for Diagnosis, Monitoring and Drug Resistance Mutation Detection in Chronic Myelogenous Leukemia. The FEP Medical Policy Manual can be found at: www.fepblue.org

### III. DESCRIPTION/BACKGROUND

**Chronic Myelogenous Leukemia**
Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within 3 to 5 years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, very high or very low platelet counts, etc.1 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 concerning 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 younger than 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past several decades, primarily in children, largely due to advances in the understanding of the molecular genetics of the disease, the incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of about 80%. The long-term prognosis among adults is poor, with cure rates of 30% to 40%, explained, in part, by different subtypes among age groups, including the BCR-ABL fusion gene, which has a poor prognosis and is much less common in childhood ALL, as compared with adult ALL.

**Disease Genetics**

Philadelphia chromosome (Ph)–positive leukemias are characterized by the expression of the oncogenic fusion protein product Bcr-Abl1, resulting from reciprocal translocation between chromosomes 9 and 22. This abnormal fusion 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, as this information is necessary for
subsequent quantitative testing of fusion gene messenger RNA transcripts. If the fusion gene is not confirmed, then the diagnosis of CML is called into question.

Determining the qualitative presence of the \textit{BCR-ABL1} fusion gene is not necessary to establish a diagnosis of ALL.

\textbf{Treatment and Response and Minimal Residual Disease}

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

Quantitative determination of \textit{BCR-ABL1} transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment. Evaluation of trial samples has consistently shown that the degree of molecular response correlates with risk of progression. In addition, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising \textit{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®), a tyrosine kinase inhibitor (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.”\textsuperscript{3} 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 CR, significantly lower than that achieved in Ph-negative ALL.\textsuperscript{4} The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.\textsuperscript{4}

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percent of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib.\textsuperscript{3} 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 (MRD.) Among children with ALL who achieve a complete response by morphologic evaluation after induction therapy, approximately 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (which affords a sensitivity of MRD detection of 0.01%), or PCR‒based analyses (Ig and T-cell receptor gene rearrangements or analysis of \textit{BCR-ABL} transcripts), which
are the most sensitive method of monitoring treatment response, with a sensitivity of 0.001%. Ig and T-cell receptor gene arrangement analysis is applicable for most ALL patients, whereas PCR analysis of BCR-ABL transcripts is applicable only in Ph-positive patients.

**Resistance**

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

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

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

**Molecular Resistance**

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

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1 Note that new BCR-ABL KD mutations also occur in about 80% to 90% of cases of acute lymphoblastic leukemia in relapse after TKI treatment, and in CML blast transformation.
The presence of ABL kinase domain point mutations are associated with treatment failure; a large number of mutations have been detected, but extensive analysis of trial data with low-sensitivity mutation detection methods has identified a small number of mutations that are consistently associated with treatment failure with specific TKIs; guidelines recommend testing for, and using information regarding these specific mutations in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples that need to be sequenced. Targeted methods that detect the mutations of interest for management decisions are also acceptable if designed for low sensitivity. High sensitivity assays are not recommended.

Compared with imatinib, fewer mutations are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al. and Cortes et al. studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell \( \text{BCR-ABL1} \) mutations. However, neither dasatinib nor nilotinib are effective against resistant clones with the \( T315I \) mutation, and new agents and treatment strategies are in development for patients with \( T315I \) resistance.

In a recent follow-up study of nilotinib by le Coutre et al., 137 patients with accelerated phase CML were evaluated after 24 months. Sixty-six percent of patients maintained major cytogenetic responses at 24 months. The estimates of overall and progression-free survival rates at 24 months were 70% and 33%, respectively. Grade 3/4 neutropenia and thrombocytopenia were each observed in 42% of patients.

Rarely, other acquired cytogenetic abnormalities such as \( \text{BCR-ABL} \) 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.

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 \( \text{BCR-ABL} \) level while in hematologic complete response or clinical relapse warrants mutational analysis.

### Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The \( \text{BCR/ABL1} \) qualitative and quantitative genotyping tests and \( \text{ABL} \) KD mutation tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
IV. RATIONALE

Various types of laboratory tests involving *BCR-ABL1* detection are associated with chronic myelogenous leukemia (CML) and have different clinical uses. Briefly, these are:

1. **Diagnosis:** patients who do not have the *BCR-ABL1* 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 mutations for drug resistance at response failure/disease progression; various test technologies are in use (not standardized).

**Diagnosis/Pretreatment Work-Up**

**Chronic Myelogenous Leukemia**

While the diagnosis of CML is based on the presence of characteristic cellular abnormalities in bone marrow, the presence of the Philadelphia chromosome (Ph) and/or confirmation of the *BCR-ABL1* fusion gene is essential to diagnosis. The initial evaluation of chronic phase CML should include bone marrow cytogenetics, not only to detect the Ph chromosome, but to detect other possible chromosomal abnormalities. If bone marrow is not available, FISH analysis with dual probes for *BCR* and *ABL* genes or qualitative RT-PCR can provide qualitative confirmation of the fusion gene and its type. Baseline measurement of *BCR-ABL* transcript levels are recommended as part of the initial evaluation, providing confirmation of the fusion gene, ensuring that it is detectable (rare variants requiring nonstandard probes may occur), as well as a baseline for monitoring response to treatment.

**Acute Lymphoblastic Leukemia**

The diagnosis of acute lymphoblastic leukemia (ALL) is made by demonstrating 20% or greater bone marrow lymphoblasts and demonstration that the *BCR-ABL* fusion gene is not essential to diagnosis; 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/Disease Remission

Chronic Myelogenous Leukemia
Quantitative RT-PCR measurement of BCR-ABL1 RNA transcript levels is the method of choice for measuring response to treatment because of the high sensitivity of the method and strong correlation with outcomes. Compared with conventional cytogenetics, quantitative RT-PCR (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 (not from the actual baseline level of the individual patient). Results from the 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 compared with 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. 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, molecular response to treatment be measured every 3 months for 2 years, then every 3 to 6 months thereafter. Without complete cytogenetic response (CCyR), 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 as well, and will likely also be applied to bosutinib and ponatinib.

Rising BCR-ABL1 transcript levels are associated with increased risk of mutations and of treatment failure. However, the amount of rise that is considered clinically significant for considering mutation 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 2- to 10-fold increases, and increases of 0.5-1 log. 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 mutation 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 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 (available online at http://www.whereareyouontheis.com/Default.aspx). 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.

**Acute Lymphoblastic Leukemia**

Despite significantly higher complete response (CR) rates with the use of tyrosine kinase inhibitors (TKIs) in Ph-positive ALL, the response is typically short-lived and relapses are common. The principal aim of post remission therapy is eradicating minimal residual disease (MRD), which is the prime cause for relapse. Studies in both 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 CR 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 by 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% (±0.9%).

NCCN recommendations state that the timing of when to test for MRD depends on the ALL chemotherapy regimen used and may occur during or after completion of induction therapy, and at additional time points depending on the chemotherapy regimen used.

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 stem cell transplantation, whereas achievement of MRD negativity may be an indication for chemotherapy.
Identification of ABL Kinase Domain Mutations (Mutations Associated With TKI Resistance)

Chronic Myelogenous Leukemia
Screening for BCR-ABL1 kinase domain (KD) point mutations (ie, single nucleotide polymorphisms) in chronic phase CML is recommended for patients with inadequate initial response to TKI treatment, those with evidence of loss of response, and for patients who have progressed to accelerated or blast phase CML. The purpose of testing for KD point mutations is, in the setting of potential treatment failure, to help select among other possible TKI treatments or allogeneic stem cell transplantation. The following discussion focuses only on KD point mutations.

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 mutation does not predict differential response to TKI therapy, although the presence of the T315I mutation uniformly predicts TKI failure. However, during the public comment period, the review was strongly criticized by respected pathology organizations for lack of attention to several issues that were subsequently insufficiently addressed in the final report. Importantly, the review grouped together studies that used KD mutation screening methods with those that used targeted methods, and grouped together studies that used mutation detection technologies with very different sensitivities. The authors dismissed the issues as related to analytic validity and beyond the scope of the report. However, in this clinical scenario assay with different intent (screening vs targeted) and assays of very different sensitivities may lead to different clinical conclusions and an understanding of these points is critical.

Point Mutation Detection Methods
Currently, methods for detecting drug resistance mutations are not standardized; clinical laboratories may choose among several different methods. The methods can detect either specific, known mutations (eg, targeted mutation analysis) or screen for all possible mutations (eg, direct sequencing); sensitivity also varies by method.

The particular methods to detect BCR-ABL KD mutations will have great influence on the detection frequency, analytic sensitivity and the clinical impact of testing. The various mutation detection methods available have widely different analytic sensitivities, from the least sensitive direct Sanger sequencing to the highly sensitive mutation-specific quantitative PCR methods.

Direct Sanger sequencing screens for all possible mutations but has low sensitivity, detecting a mutation present in approximately 1 in 5 BCR-ABL1 transcripts. Denaturing high-performance liquid chromatography (DHPLC) is also a screening method with initially higher sensitivity to detect the presence or absence of any mutations. Follow-up Sanger sequencing of positive samples is required to identify the mutations present; final sensitivity of this method is the sensitivity of sequencing. Targeted methods, used either to screen for only the most common, clinically relevant mutations or to monitor already identified mutations after a therapy change,
can offer either limited sensitivity (eg, pyrosequencing) or very high sensitivity (eg, allele-specific PCR).

**KD Point Mutations and Treatment Outcomes**

Branford et al\(^4\) have summarized much of the available evidence regarding KD mutations detected at imatinib failure, and subsequent treatment success or failure with dasatinib or nilotinib. The studies referenced used direct Sanger sequencing, with or without DHPLC screening, to identify mutations at low sensitivity. The authors conducted a survey of mutations detected in patients at imatinib failure at their own institution and compared it with a collation of mutations derived from the literature. For both, the \textit{T315I} mutation was most common; although about 100 mutations have been reported, the 7 most common (at residues \textit{T315}, \textit{Y253}, \textit{E255}, \textit{M351}, \textit{G250}, \textit{F359}, and \textit{H396}) accounted for 60\% to 66\% of all mutations in both surveys.

Detection of the \textit{T315I} mutation at imatinib failure is associated with lack of subsequent response to high-dose imatinib, or to dasatinib or nilotinib. For these patients, allogeneic stem cell transplantation remained the only available treatment until the advent of new agents such as ponatinib.\(^4\) Most common, however, does not necessarily correspond to clinically significant. Based on the available clinical studies, most imatinib-resistant mutations remain sensitive to dasatinib and nilotinib. However, preexisting or emerging mutations \textit{T315A}, \textit{F317L/I/V/C}, and \textit{V299L} are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging mutations \textit{Y253H}, \textit{E255K/V}, and \textit{F359V/C} have been reported for decreased clinical efficacy with nilotinib treatment following imatinib failure. In the survey reported by Branford et al, a total of 42\% of patients tested had \textit{T315I} or one of these dasatinib- or nilotinib-resistant mutations.\(^4\) As a result, guidelines recommend mutation analysis only at treatment failure, and use of the \textit{T315I} mutation and the identified dasatinib- and nilotinib-resistant mutations to select the subsequent treatment.\(^3,39\) In the absence of any of these actionable mutations, various treatment options are available. Note that these data have been obtained from studies in which patients were all initially treated with imatinib. No data are available regarding mutations developing during first-line therapy with dasatinib or nilotinib.\(^4\)

\textit{ABL} KD mutational 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 \textit{BCR-ABL1} transcript ratio and therefore loss of major molecular response). Mutation testing is also recommended for progression to accelerated or blast phase CML. Treatment recommendations based on mutation(s) are shown in Table 1.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Recommendation</th>
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<tbody>
<tr>
<td>\textit{T315I}</td>
<td>Ponatinib, HSCT, or clinical trial</td>
</tr>
<tr>
<td>\textit{V299L, T315A, F317L/I/V/C}</td>
<td>Consider nilotinib or bosutinib(^*) rather than dasatinib</td>
</tr>
<tr>
<td>\textit{Y253H, E255K/V, F359V/C/I}</td>
<td>Consider dasatinib or bosutinib(^*) rather than nilotinib</td>
</tr>
</tbody>
</table>
Because only a small number of mutations have been recommended as clinically actionable, targeted assays may also be used to screen for the presence of actionable mutations at treatment failure. Quantitative, targeted assays may also be used to monitor levels of already identified clinically significant mutations after starting a new therapy following initial treatment failure. Targeted assays use different technologies, which can be made very sensitive to 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 mutations that predict treatment failure well in advance of clinical indications. While some results have been positive, not all mutations detected in advance predict treatment failure, and more study is recommended before these assays are used for monitoring in advance of treatment failure. A direct correlation of low-sensitivity and high-sensitivity assays and a limited correlation with clinical outcomes support recommendations of sequencing, with or without DHPLC screening, for identification of mutations. Although high-sensitivity assays identified more mutations than did sequencing, the clinical impact of the additional mutations was viewed as uncertain.

Other types of mutations in addition to point mutations 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 mutations is not recommended.

Acute Lymphoblastic Leukemia
Unlike in CML, resistance in ALL to TKIs is less well studied. Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or by competition of other coexisting subclones. In patients with ALL who are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

### Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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<tr>
<td>NCT01343173</td>
<td>Multicenter Trial Estimating the Persistence of Molecular Remission in Chronic Myeloid Leukaemia in Long Term After Stopping Imatinib</td>
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<td>Jul 2017</td>
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<td>NCT01578213</td>
<td>Validation of Digital-PCR Analysis Through Programmed Imatinib Interruption in PCR Negative CML Patients (ISAV)</td>
<td>100</td>
<td>Nov 2018</td>
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</table>
Summary of Evidence

The evidence for BCR/ABL1 qualitative RT-PCR testing for the presence of the fusion gene for diagnosis in individuals with suspected chronic myelogenous leukemia (CML) and quantitative RT-PCR to establish baseline for monitoring treatment response in CML and acute lymphoblastic leukemia (ALL) includes validation studies. Relevant outcomes are test accuracy and test validity. The sensitivity of testing with RT-PCR is high compared with conventional cytogenetics. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for quantitative BCR/ABL1 testing for monitoring of CML and ALL treatment response and remission in individuals with a diagnosis of CML or ALL includes a randomized trial and case series. Relevant outcomes are disease-specific survival, test accuracy, 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 risk of disease progression and survival, and may stratify patients to different treatment options. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for evaluation of ABL kinase domain (KD) point mutations to evaluate patients for tyrosine kinase inhibitor resistance in individuals who have a diagnosis of CML or ALL includes a systematic review on pharmacogenetic testing for TKIs and case series that reported the presence of KD mutations detected at imatinib failure. Relevant outcomes are test accuracy, test validity and medication use. Studies have shown a correlation between certain types of mutations and treatment response and the use in selecting subsequent treatment options. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network (NCCN) practice guidelines (v.1.2016) chronic myelogenous leukemia outline recommended methods for diagnosis and treatment management of CML, including BCR-ABL1 tests for diagnosis, monitoring, and ABL kinase domain.
mutations, and were referred to extensively in this document.\(^3\) The European LeukemiaNet management recommendations for CML are similar to those of NCCN and have also been cited in this document.\(^{31,38}\) The U.S. Association for Molecular Pathology\(^6\) and European LeukemiaNet recommendations for KD mutation analysis\(^{39}\) have been referenced; both provide very similar guidelines.

The NCCN practice guidelines (v.2.2015) acute lymphoblastic leukemia state that, if minimal residual disease (MRD) is being evaluated, the initial measurement should be performed on completion of induction therapy; additional time points for MRD evaluation may be useful, depending on the specific treatment protocol or regimen used. MRD is an essential component of patient evaluation over the course of sequential therapy. If a patient is not treated in an academic center, there are commercially available tests available for MRD assessment.\(^{54}\)

In 2010, recommendations were published on the technical requirements for MRD assessment and definitions for response based on MRD results, as a result of a consensus development meeting.\(^{55}\) The recommendations were made in an effort to standardize MRD measurements and MRD data reporting in European ALL trials.

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

Not applicable.

**Medicare National Coverage**

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

V. **DEFINITIONS**

NA

VI. **BENEFIT VARIATIONS**

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. **DISCLAIMER**
Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
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<tbody>
<tr>
<td>81170</td>
<td>81206</td>
</tr>
<tr>
<td>81207</td>
<td>81208</td>
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<tr>
<td>81401</td>
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<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia not having achieved remission</td>
</tr>
<tr>
<td>C91.01</td>
<td>Acute lymphoblastic leukemia, in remission</td>
</tr>
<tr>
<td>C91.02</td>
<td>Acute lymphoblastic leukemia, in relapse</td>
</tr>
<tr>
<td>C92.10</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission</td>
</tr>
<tr>
<td>C92.11</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in remission</td>
</tr>
<tr>
<td>C92.12</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in relapse</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

<table>
<thead>
<tr>
<th>Policy Title</th>
<th>BCR-ABL1 TESTING IN CHRONIC MYELOGENOUS LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA</th>
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</thead>
<tbody>
<tr>
<td>Policy Number</td>
<td>MP-2.317</td>
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</tbody>
</table>


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


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


**Policy Title:** BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

**Policy Number:** MP-2.317

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**Other:**


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**X. Policy History**

<table>
<thead>
<tr>
<th>MP 2.317</th>
<th>Date</th>
<th>Description</th>
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<tr>
<td><strong>CAC 7/30/13</strong></td>
<td>New policy. BCBSA adopted. BCR/ABL1 qualitative testing for the presence of the fusion. Policy coded.</td>
<td></td>
</tr>
<tr>
<td><strong>7/24/14</strong></td>
<td>Administrative change for the Medicare variation - For Novitas MAC jurisdictions, the LCD has been assigned a new number. Biomarkers for Oncology LCD changed from L33124 to L34796</td>
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<tr>
<td><strong>CAC 5/20/14 Minor.</strong></td>
<td>Policy statements added for ALL, medically necessary prior to initiation of treatment, for disease monitoring and to evaluate for TKI resistance. Title also changed to add ALL. Formerly BCR-ABL1 Testing in Chronic Myelogenous Leukemia. Coding reviewed.</td>
<td></td>
</tr>
<tr>
<td><strong>CAC 6/2/15 Consensus review.</strong></td>
<td>No changes to the policy statements. Language added to the policy guideline section to clarify the timing of testing in patients who are responding to treatment or who have a complete cytogenetic response. References and rationale updated. Policy coded.</td>
<td></td>
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<tr>
<td><strong>11/2/15 Administrative change.</strong></td>
<td>LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.</td>
<td></td>
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<tr>
<td><strong>Administrative 1/20/16:</strong></td>
<td>Added new 2016 code (81170).</td>
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</table>
BCR-ABL1 TESTING IN CHRONIC MYELOGENOUS LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA

CAC 5/31/16 Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.

Admin update 1/1/17: Product variation section reformatted.

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