MEDICAL POLICY

POLICY TITLE	**BCR-ABL1 TESTING IN CHRONIC MYELOGENOUS LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA**
POLICY NUMBER	**MP 2.317**

CLINICAL BENEFIT	☐ **MINIMIZE SAFETY RISK OR CONCERN.** ☐ **MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS.** ☐ **ASSURE APPROPRIATE LEVEL OF CARE.** ☐ **ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS.** ☒ **ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET.** ☐ **ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.**
Effective Date:	**RETIRED 7/1/2026**

POLICY

Chronic Myeloid Leukemia (CML)

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

Evaluation of *ABL* kinase domain point mutations to evaluate individuals for tyrosine kinase inhibitor resistance may be 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 general 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) may be 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 individuals for tyrosine kinase inhibitor resistance may be 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 general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Diagnosis of Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Qualitative molecular confirmation of the cytogenetic diagnosis (i.e., detection of the Philadelphia chromosome) is necessary for accurate diagnosis of chronic myelogenous leukemia (CML). Identification of the Philadelphia chromosome is not necessary to diagnose acute lymphoblastic leukemia (ALL); however, molecular phenotyping is usually performed at the initial assessment.

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

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

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

More frequent monitoring is indicated for patients diagnosed with CML who are in complete molecular remission and are not undergoing treatment with a tyrosine kinase inhibitor (TKI).

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

Tyrosine Kinase Inhibitor Resistance

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

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

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

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

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

DESCRIPTION/BACKGROUND

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic cells, accounting for 15% of adult leukemias. The t(9,22) reciprocal translocation is the basis of pathology, diagnosis, and monitoring in CML. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within 3 to 5 years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, or very high or very low platelet counts. From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow.

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

Chronic myeloid leukemia (CML) and a subset of acute lymphoblastic leukemias (ALL) are collectively termed “Philadelphia chromosome-positive (Ph+)” leukemias because they share a common pathogenetic lesion, the Philadelphia (Ph) chromosome. This chromosome results from a reciprocal translocation between chromosomes 9 and 22. On the Ph chromosome, a

BCR-ABL1 fusion gene is formed that encodes a tyrosine kinase whose deregulated activity may be therapeutically targeted. Since 2003, the incorporation of tyrosine kinase inhibitors (TKIs) in the front-line treatment protocols has significantly improved the prognosis of both diseases and has shifted treatment endpoints from hematologic and cytogenetic responses to molecular responses.

The Philadelphia chromosome characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as *BCR-ABL1,* are more common. In ALL, the Ph chromosome is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is associated with ALL, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain (KD) of the BCR-ABL protein is the same as the KD of the normal ABL protein. However, the abnormal BCR-ABL protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Diagnosis

Although CML is diagnosed primarily by clinical and cytogenetic methods, qualitative molecular testing is needed to confirm the presence of the *BCR-ABL1* fusion gene. If the Ph chromosome is not found, the type of fusion gene needs to be identified. 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.

Standardization of BCR-ABL1 Quantitative Transcript Testing

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.

A substantial effort has been made to standardize the *BCR-ABL1* qRT-PCR testing and reporting across academic and private laboratories. In 2006, the National Institute of Health Consensus Group proposed an IS for *BCR-ABL1* measurement. The IS defines 100% as the median pretreatment baseline level of *BCR-ABL1* RNA in early chronic phase CML; as determined in the pivotal IRIS trial, major molecular response 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 (e.g., *ABL*) to control for the quality and quantity of RNA and to normalize for potential differences between tests.

Treatment and Response and Minimal Residual Disease

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

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

Three generations of tyrosine kinase inhibitors (TKIs) are now available for the treatment of CML patients. Thanks to their remarkable efficacy, most CML patients face a near-normal life expectancy and a non-negligible proportion of them may even discontinue the treatment, achieving so-called “treatment-free remission” (TFR)

Imatinib (Gleevec; Novartis), a tyrosine kinase inhibitor (TKI), was originally developed specifically to target and inactivate the Abl tyrosine kinase portion of the Bcr-Abl1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in “durable responses in [a] large proportion of the patients with a decreasing rate of relapse.” As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60% to 80% of patients achieving a complete response, significantly lower than that achieved in Ph-negative ALL. The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percentage of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib.[1] It is well established that most “good responders” who are considered to be in morphologic remission, but relapse may still have considerable levels of leukemia cells, referred to as minimal residual disease (MRD). Among children with ALL who achieve a complete response by morphologic evaluation after induction therapy, 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (sensitivity of MRD detection, 0.01%), or polymerase chain reaction-based analyses (Ig and T-cell receptor gene rearrangements or analysis of *BCR-ABL* transcripts), which are the most sensitive methods of monitoring treatment response (sensitivity, 0.001%).[1] 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 usually does not completely eradicate malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. Also, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. The molecular basis for resistance is explained in the following section. When the initial response to treatment is inadequate or there is a loss of response, resistance variant analysis is recommended to support a diagnosis of resistance (based on hematologic or cytogenetic relapse) and to guide the choice of alternative doses or treatments.

Structural studies of the Abl-imatinib complex have resulted in the design of second-generation Abl inhibitors, including dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis), which were initially approved by the U.S. Food and Drug Administration for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of both agents in newly diagnosed chronic phase patients have shown that both are superior to imatinib for all outcomes measured after 1 year of treatment, including complete cytogenetic response (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis. Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. The Food and Drug Administration (FDA) has approved third-generation TKIs, ponatinib and bosutinib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI is indicated. Bosutinib is indicated for Ph-positive CML with resistance or intolerance to prior therapy.

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

Molecular Resistance

Molecular resistance is most often explained as genomic instability associated with the creation of the abnormal *BCR-ABL1*gene, usually resulting in point mutations 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.) 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 drug resistance.

Other acquired cytogenetic abnormalities such as *BCR-ABL* gene amplification and protein overexpression have also been reported. Resistance unrelated to kinase activity may result from additional oncogenic activation or loss of tumor suppressor function, and may be accompanied by additional karyotypic changes. Resistance in ALL to TKIs is less well studied. In patients with ALL receiving a TKI, a rise in the *BCR-ABL* level while in hematologic complete response or clinical relapse warrants variant analysis.

Regulatory Status

On September 2019, the Xpert BCR-ABL Ultra Test was approved for use on the GeneXpert® Dx System, GeneXpert® Infinity Systems (Cepheid) by the FDA through the 510(k) pathway (K190076). The test may be used in patients diagnosed with t(9;22) positive CML expressing BCR-ABL1 fusion transcripts type e13a2 and/or e14a2. The test utilizes RT-qPCR.

On February 2019, the QXDx BCR-ABL % IS Kit (Bio-Rad Laboratories) was approved by the FDA through the 510(k) pathway (K181661). This droplet digital PCR (ddPCR) test may be used in patients with diagnosed t(9;22) positive CML, during monitoring of treatment with TKIs, to measure BCR-ABL1 to ABL1 mRNA transcript levels, expressed as a log molecular reduction value from a baseline of 100% on the IS. This test is not intended to differentiate between e13a2 or e14a2 fusion transcripts and is not intended for the diagnosis of CML. This test is intended for use only on the Bio-Rad QXDx AutoDG ddPCR System. FDA classification code: OYX.

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 to diagnose 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 diagnosed with 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, FDA has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have suspected CML who receive *BCR-ABL1* fusion gene qualitative testing to confirm the diagnosis and establish a baseline for monitoring treatment, the evidence includes validation studies. Relevant outcome is test validity. The sensitivity of testing with RT-PCR 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 with inadequate initial response, loss of response, and/or disease progression who receive an evaluation for *ABL* KD SNVs to assess for TKI resistance, the evidence includes a systematic review and case series. Relevant outcomes are disease-specific survival, test validity, and medication use. The systematic review and case series evaluated pharmacogenetics testing for TKIs and reported the presence of KD 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 Philadelphia 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 disease-specific survival, test validity, and change in disease status. 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 Philadelphia chromosome-positive ALL and signs of treatment failure or disease progression who receive an evaluation for *ABL1* KD 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.

DEFINITIONS

N/A

I. DISCLAIMER

TOP

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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:

Procedure Codes								
81170	81206	81207	81208	81401	0016U	0040U		

ICD-10-CM Diagnosis Codes	Description
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse

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POLICY HISTORY

MP 2.317	**04/24/2020 Consensus Review**. No change to policy statements. References updated.
	04/30/2021 Consensus Review. No change in policy statement. Policy guidelines updated. References updated. Code 0016U added. NCCN statement added to policy.
	11/21/2022 Consensus Review. No change to policy statement. Updates to background and references.

	12/29/2023 Consensus Review. No change to policy statement. Updated references.
	11/12/2024 Consensus Review. No change to policy statement. Removed NCCN statement. Updated references.
	12/02/2025 Consensus Review. No change to policy statement. Updated references.
	03/17/2026 Retirement Review.