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

Policy # 00428
Original Effective Date: 07/16/2014
Current Effective Date: 01/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia is addressed separately in medical policy 00048.

When Services Are Eligible for Coverage

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

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

Chronic Myelogenous Leukemia

When Services Are Eligible for Coverage

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

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

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

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

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

When Services Are Considered Investigational

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

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

Acute Lymphoblastic Leukemia

When Services Are Eligible for Coverage

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

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

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

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

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Note:
When coverage criteria are met for BCR/ABL1 testing, tissue-based (bone marrow), or alternatively peripheral blood (if detectable circulating lymphoblasts) somatic genetic testing using 50 or less gene panel can be considered for coverage for children and adults with ALL to establish the diagnosis or to identify actionable therapeutic targets at time of diagnosis. A multi-gene panel needs to contain at a minimum the following genes: ABL1, ABL2, CRLF2r, JAK 1/2/3, SH2B3, IL7R, PDGFRA, PDGFRB, FLT3r, TP53, IKZF1. In this situation a multi-gene panel will be approved when billed with a single panel CPT code (i.e., 81450).

When Services Are Considered Investigational

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

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

Policy Guidelines

Diagnosis of Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
Qualitative molecular confirmation of the cytogenetic diagnosis (ie, detection of the Philadelphia chromosome) is necessary for accurate diagnosis of 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 (see Determining Baseline RNA Transcript Levels and Subsequent Monitoring subsection).

Distinction between molecular variants (ie, p190 vs p210) is necessary for accurate results in subsequent monitoring assays.

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

For CML, testing is appropriate at baseline before the start of imatinib treatment, and testing is appropriate every 3 months when the individual 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 3-month intervals during treatment 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 individuals 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 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 individuals with ALL receiving a TKI, a rise in the *BCR-ABL* mRNA level while in hematologic complete response or clinical relapse warrants variant analysis.

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

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

Background/Overview

Myelogenous Leukemia and Lymphoblastic Leukemia
Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within 3 to 5 years to the accelerated or blast phase. Multiple sets of criteria defining accelerated phase CML have evolved in recent decades, and may include 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, presence of an additional clonal cytogenetic abnormality in CML cells, 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 acute leukemia, with rapid progression and short survival. Similar to accelerated phase, multiple sets of criteria have been developed for the diagnosis of blast phase CML, and may include more than 20% myeloblasts in the blood or bone marrow, morphologically apparent lymphoblast proliferation , 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 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 17 years; more than 50% of patients are diagnosed before 20 years of age. Survival rates for patients with ALL have improved dramatically, particularly 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 more than 80%. Long-term prognosis among adults is poor, with overall cure rates of 30% to 40%. Prognosis variation is explained, in part, by different subtypes among age groups, including the *BCR-ABL* fusion gene, which has a poor prognosis and is much less common in childhood ALL.

Disease Genetics

Philadelphia (Ph) chromosome-positive leukemias are characterized by the expression of the oncogenic fusion protein product BCR-ABL1, resulting from a reciprocal translocation between

chromosomes 9 and 22. This abnormal fusion product characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as *BCR-ABL1*, are more common. In ALL, the Ph chromosome is found in approximately 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, abnormal BCR-ABL protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Diagnosis

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

Determining the qualitative presence of the *BCR-ABL1* fusion gene is not necessary to establish a diagnosis of ALL, and is instead used for risk stratification and treatment decisions in this setting.

Standardization of* BCR-ABL1 *Quantitative Transcript Testing

A substantial effort has been made to standardize the *BCR-ABL1* quantitative reverse transcription-polymerase chain reaction 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 International Randomized Study of Interferon versus STI571 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 (eg, *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 the risk of progression. Also, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising *BCR-ABL1* transcript levels predict treatment failure and the need to consider a change in management. Quantitative polymerase chain reaction-based methods and international standards for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec; 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 response in a large proportion of patients. As a result, imatinib, and, subsequently, newer-generation TKIs, became the primary therapy for most patients with newly diagnosed chronic phase CML. More recent studies have demonstrated that treatment-free remission (ie, discontinuation of certain TKIs) is safe and feasible in select patients with a stable molecular response of sufficient depth.

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 addition of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.

Treatment response in Ph-positive ALL is evaluated initially by the hematologic and morphologic response (normalization of peripheral blood counts with trilineage hematopoiesis, <5% bone marrow blasts, and absence of circulating blasts and extramedullary disease), then by flow cytometry or molecular pathology. It is well established that most “good responders” who are considered to be in morphologic remission may still have considerable levels of leukemia cells, referred to as minimal (or measurable) 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 next-generation sequencing or polymerase chain reaction-based molecular analyses (eg, Ig and T-cell receptor gene rearrangements, sequencing of fusion genes, or analysis of *BCR-ABL* transcripts), the latter of which are the most sensitive methods of monitoring treatment response (sensitivity, 0.0001%).

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 with imatinib or another front-line TKI is inadequate or there is a loss of response, resistance variant analysis is recommended to support a diagnosis of resistance (based on hematologic, cytogenetic, and/or molecular relapse) and to guide the choice of alternative doses or treatments.

Structural studies of the ABL -imatinib complex have resulted in the design of newer -generation ABL inhibitors, including bosutinib (Bosulif; Pfizer), dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis), 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 these agents in newly diagnosed chronic-phase patients have demonstrated superiority to imatinib for outcomes including complete cytogenetic response, major molecular response, time to remission, and/or rates of progression to accelerated phase or blast crisis, leading to their approval for front-line chronic phase use. The FDA has also approved the third-generation TKI ponatinib and the allosteric ABL1 inhibitor asciminib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI is indicated, while asciminib is indicated for the treatment of chronic-phase CML in patients with T315I or who have received prior treatment with ≥2 TKIs.

There is no strong evidence to recommend specific treatment changes on the sole basis of rising *BCR-ABL1* transcripts detected by quantitative polymerase chain reaction.

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. 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 (ie, active site) of the protein. Some variants are associated with moderate resistance and are responsive to higher doses of TKIs, while other variants may not be clinically significant. Two variants, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance.

The presence of *ABL* SNVs is associated with treatment failure. A large number of variants have been detected, but extensive analysis of trial data with low-sensitivity variant detection methods has identified a 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 consensus-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 bosutinib, 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 bosutinib, dasatinib, nor nilotinib are effective against resistant clones with the T315I variant. Other treatment strategies are in development for patients with drug resistance.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 the 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 the 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, the FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 (KD) single nucleotide variants related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

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 an 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 systematic review and nonrandomized trials. Relevant outcomes are disease-specific survival, test validity, and change in disease status. Studies have shown 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 an improvement in the net health outcome.

For individuals who have a diagnosis of CML with an inadequate initial response, loss of response, and/or disease progression who receive an evaluation for *ABL* KD single nucleotide variants to assess for TKI resistance, the evidence includes a systematic review and retrospective cohort study. 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 single nucleotide variants 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 an improvement in the net health outcome.

For individuals who have a diagnosis of Ph-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 prospective and retrospective cohort studies and case series. Relevant outcomes are disease-specific survival, test validity, and change in disease status. As with CML, studies have shown 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 an improvement in the net health outcome.

For individuals who have Ph-positive ALL and signs of treatment failure or disease progression who receive an evaluation for *ABL1* KD single nucleotide variants 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 1 or more of the second-generation TKIs; these variants are used to guide medication selection. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network practice guidelines (v. 1.2024) on chronic myeloid leukemia outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, 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 the first 6 months following discontinuation, bimonthly during months 7-12, and quarterly thereafter (indefinitely) for patients who demonstrate BCR-ABL1 ≤0.01% International Scale (IS).

Table 1. Treatment Options for CML Based on *BCR-ABL1* Variant Profile[i,ii]

Contraindicated Single Nucleotide Variants	Treatment
None	Ponatinib, omacetaxine, or allogeneic HCT
T315I, Y253H, E255K/V, F359V/C/I	Nilotinib
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315I, V299L, G250E, F317L	Bosutinib
A337T, P465S, or F359V/I/C	Asciminib

CML: chronic myelogenous leukemia; HCT: hematopoietic cell transplantation.

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The National Comprehensive Cancer Network practice guidelines v. 2.2023 (NCCN) recommends for diagnosis of acute lymphoblastic leukemia (ALL), molecular characterization for optimal risk stratification and treatment planning, testing bone marrow or peripheral blood lymphoblasts using comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations (list of cytogenetic and molecular alterations in ALL-3).

The NCCN on ALL also state that, if minimal residual disease is being evaluated, the initial measurement should be performed on completion of initial induction therapy; additional time points for minimal residual disease evaluation may be useful, depending on the specific treatment protocol or regimen used. Serial monitoring frequency may be increased in individuals with molecular relapse or persistent disease. Minimal residual disease is an essential component of patient evaluation during sequential therapy. Treatment options based on *BCR-ABL* Mutation Profile are shown in Table 2.

Table 2. Treatment Options for ALL Based on *BCR-ABL1* Variant Profile[i,ii]

Contraindicated Single Nucleotide Variants	**Treatment**
None	Ponatinib
T315I, Y253H, E255K/V, F359V/C/I, G250E	Nilotinib
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315I, V299L, G250E, F317L	Bosutinib

ALL: acute lymphoblastic leukemia.

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[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03874858[a]	A Phase II, Single-arm, Multicenter Study of Full Treatment-free Remission in Patients With Chronic Myeloid Leukemia in Chronic Phase Treated With Nilotinib in First-line Therapy Who Have Achieved a Sustained, Deep Molecular Response for at Least 1 Year	103	Jul 2026 (recruiting)
NCT03817398	Stopping Tyrosine Kinase Inhibitors (TKI) to Assess Treatment-Free Remission (TFR) in Pediatric Chronic Myeloid Leukemia - Chronic Phase (CML-CP)	110	Jun 2026 (recruiting)
NCT02602314	Sustained Treatment-free Remission in BCR-ABL+ Chronic Myeloid Leukemia: a Prospective Study Comparing Nilotinib Versus Imatinib With Switch to Nilotinib in Absence of Optimal Response (SUSTRENIM)	450	Feb 2024 (ongoing)

NCT01784068[a]	A Single-arm, Multicenter, Nilotinib Treatment-free Remission Study in Patients With BCR-ABL1 Positive Chronic Myelogenous Leukemia in Chronic Phase Who Have Achieved Durable Minimal Residual Disease (MRD) Status on First Line Nilotinib Treatment (ENESTFreedom)	215	Feb 2025 (ongoing)
NCT01698905[a]	A Phase II, Single-Arm, Open Label Study of Treatment-free Remission in Chronic Myeloid Leukemia (CML) Chronic Phase (CP) Patients After Achieving Sustained MR4.5 on Nilotinib	163	Feb 2025 (ongoing)
NCT02881086	Treatment Optimization in Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma by Individualized, Targeted and Intensified Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients	900	Jul 2025 (ongoing)
NCT03589326[a]	A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced-Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)	230	Jul 2027 (recruiting)
Unpublished			
NCT03421626[a]	Clinical Evaluation of the Xpert BCR-ABL Ultra Assay on the GeneXpert Instrument Systems	266	Aug 2018 (completed)
NCT02896829	Follow-up of the Persistence of the Complete Molecular Remission After Stopping Imatinib Chronic Myeloid Leukemia	97	Apr 2019 (completed)

NCT01762969	Modification of Imatinib to Other Tyrosine Kinase Inhibitors Dependent on 3-months Molecular Response of CML Patients	300	Jan 2020 (unknown)
NCT01215487[a]	A Study Investigating the Predictive Value of Philadelphia Positive Stem Cell Properties in Newly Diagnosed Patients With Chronic Myeloid in Chronic Phase Receiving Treatment With Imatinib	68	May 2020 (completed)
NCT02546674[a]	A Phase IV Single-Arm, Multicenter, Open-label Study Assessing Deep Molecular Response in Adult Patients With Newly Diagnosed Philadelphia Chromosome Positive CML in Chronic Phase After Two Years of Treatment With Nilotinib 300mg BID (NILOdeepR)	171	Mar 2021 (completed)
NCT03647215[a]	A Cohort Study To Establish the Prevalence of Mutations in Patients With CML Who Meet the ELN Criteria for Warning or Failure and Patients With Ph+ ALL With Detectable BCR-ABL Currently Being Treated With First or Subsequent TKI Therapy in the UK, Ireland, or France Using Next-Generation Sequencing	427	June 2021 (completed)
NCT02001818[a]	Phase II Study of Nilotinib Plus Pegylated Interferon Alfa-2b as First-line Therapy in Chronic Phase Chronic Myelogenous Leukemia Aiming to Maximize Complete Molecular Response and Major Molecular Response	100	Dec 2021 (unknown)
NCT03885830	Preliminary Evaluation of TKI Exposure-response Relationships in Real World Patients (RWPs) With Chronic Myelogenous Leukemia (CML)	45	Jun 2022 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

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07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. New policy.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2018	Coding update
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Added policy guidelines.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2022	Medical Policy Committee review

Policy # 00428
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Current Effective Date: 01/08/2024

08/10/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Statement added to policy guidelines section.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Senate bill review. Note added in coverage section.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. No change to coverage. Note and body of the policy updated.

Next Scheduled Review Date: 12/2024

Coding

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

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

Code Type	Code
CPT	0016U, 0040U, 81170, 81206, 81207, 81208, 81401 Delete code effective 01/01/2023: 81403 Add code effective 01/01/2023: 81450
HCPCS	No codes
ICD-10 Diagnosis	C91.00-C91.02, C92.10-C92.12, C92.20-C92.22

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

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

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

A. In accordance with nationally accepted standards of medical practice;

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

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

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.