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

Policy # 00428
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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 patients for tyrosine kinase inhibitor (TKI) resistance when there is inadequate initial response to treatment or any sign of loss of response; and/or when there is progression of the disease to the accelerated or blast phase to be **eligible for coverage.****

When Services Are Considered Investigational

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

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

Acute Lymphoblastic Leukemia

When Services Are Eligible for Coverage

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

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

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

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

When Services Are Considered Investigational

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

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

Policy Guidelines

Diagnosis of Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Qualitative molecular confirmation of the cytogenetic diagnosis (ie, detection of the Philadelphia chromosome) is necessary for accurate diagnosis of 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 patient is responding to treatment. After a complete cytogenetic response is achieved, testing is recommended every 3 months for 2 years, then every 3 to 6 months thereafter during treatment.

Without a complete cytogenetic response, continued monitoring at 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 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.

TKI Resistance

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

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

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

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

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology¾"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"¾to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Background/Overview

Myelogenous Leukemia and Lymphoblastic Leukemia

Chronic Myelogenous Leukemia

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

Extensive clinical data have led to the development of congruent recommendations and guidelines developed both in North America and in Europe on the use of various types of molecular tests relevant to the diagnosis and management of CML. These tests are useful in the accelerated and blast phases of this malignancy.

Acute Lymphoblastic Leukemia
ALL is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. ALL is the most common childhood tumor and represents 75% to 80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The median age at diagnosis is 14 years; 60% of patients are diagnosed at before 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past, primarily in children, largely due to a better understanding of the molecular genetics of the disease, incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of about 80%. Long-term prognosis among adults is poor, with cure rates of 30% to 40%. Prognosis variation is explained, in part, by different subtypes among age groups, including the *BCR-ABL* fusion gene, which has a poor prognosis and is much less common in childhood ALL.

Disease Genetics
Philadelphia (Ph) chromosome-positive leukemias are characterized by the expression of the oncogenic fusion protein product Bcr-Abl1, resulting from a reciprocal translocation between chromosomes 9 and 22. This abnormal fusion product characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as *BCR-ABL1,* are more common. In ALL, the Ph chromosome is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is associated with ALL, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain (KD) of the Bcr-Abl protein is the same as the KD of the normal Abl protein. However, 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.

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

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 (FDA) 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 one 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 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 (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 recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced. Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.

Unlike imatinib, fewer variants are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al (2007) and Cortes et al (2007) studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell *BCR-ABL1* variants. However, neither dasatinib nor nilotinib is effective against resistant clones with the T315I variant. Other treatment strategies are in development for patients with drug resistance.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

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.

For individuals who have suspected chronic myelogenous leukemia (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. The relevant outcome is test validity. The sensitivity of testing with reverse transcription-polymerase chain reaction is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive *BCR-ABL1* fusion gene quantitative testing at appropriate intervals for monitoring treatment response and remission, the evidence includes a systematic review and nonrandomized trials. The 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 a meaningful 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.

The 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 a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of Philadelphia chromosome-positive acute lymphoblastic leukemia 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. The 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 a meaningful improvement in the net health outcome.

For individuals who have Philadelphia chromosome-positive acute lymphoblastic leukemia 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. The 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.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network practice guidelines (v.1.2019) on chronic myelogenous 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 1 year, every 6 weeks for the second year, and every 12 weeks afterward.

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

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

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

Footnotes

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The National Comprehensive Cancer Network practice guidelines (v.2.2019) on acute lymphoblastic leukemia 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. 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. The tyrosine kinase inhibitor treatment options for acute lymphoblastic leukemia are the same as for chronic myelogenous leukemia.

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

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

ALL: acute lymphoblastic leukemia.

Footnotes

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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			
NCT00481052	The Protein Tyrosine Kinase Inhibitor Nilotinib as First-line Treatment of Ph+ Chronic Myeloid	70	Dec 2018 (ongoing)

	Leukemia (CML) in Early Chronic Phase: a Phase II Exploratory, Multicenter Study		
NCT02896829	Follow-up of the Persistence of the Complete Molecular Remission After Stopping Imatinib Chronic Myeloid Leukemia	98	Apr 2019 (ongoing)
NCT02885766[a]	A Multicenter, Open-Label Cohort Phase 1 Dose Finding Study to Evaluate Tolerability, Safety, Pharmacokinetics and Preliminary Efficacy of PF-114 Mesylate for Oral Administration in Adult Patients With Philadelphia Chromosome Positive (Ph+) Chronic Myeloid Leukemia (CML), Which is Resistant to the 2-nd Generation Bcr-Abl Inhibitors or Has T315I Mutation in the BCR-ABL Gene	44	Apr 2019 (recruiting)
NCT01578213	Validation of Digital-PCR Analysis Through Programmed Imatinib Interruption in PCR Negative CML Patients (ISAV)	100	Jun 2019 (ongoing)
NCT00471497[a]	A Phase III Multi-center, Open-label, Randomized Study of Imatinib Versus Nilotinib in Adult Patients With Newly Diagnosed Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia in Chronic Phase (CML-CP)	846	Jul 2019 (ongoing)
NCT01641107	Front-line Treatment of Philadelphia Positive/BCR-ABL Positive Acute Lymphoblastic Leukemia With Ponatinib, a New Potent Tyrosine Kinase Inhibitor	44	Nov 2019 (ongoing)
NCT01762969	Modification of Imatinib to Other Tyrosine Kinase Inhibitors Dependent on 3-months Molecular Response of CML Patients	300	Jan 2020 (recruiting)

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-ABLCurrently Being Treated With First or Subsequent TKI Therapy in the UK, Ireland, or France Using Next-Generation Sequencing	400	Jun 2020 (recruiting)
NCT01844765	A Multi-center, Open-Label, Non-controlled Phase II Study to Evaluate Efficacy and Safety of Oral Nilotinib in Pediatric Patients With Newly Diagnosed Ph+ Chronic Myelogenous Leukemia (CML) in Chronic Phase (CP) or With Ph+ CML in CP or Accelerated Phase (AP) Resistant or Intolerant to Either Imatinib or Dasatinib	59	Oct 2020 (ongoing)
NCT03885830	Preliminary Evaluation of TKI Exposure-response Relationships in Real World Patients (RWPs) With Chronic Myelogenous Leukemia (CML)	100	Dec 2020 (recruiting)
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	Apr 2021 (ongoing)
NCT01751425	Phase I-II Study of Ruxolitinib (INCB18424) for Patients With Chronic Myeloid Leukemia (CML) With Minimal Residual Disease While on Therapy With Tyrosine Kinase Inhibitors	48	Jul 2021 (ongoing)
NCT01215487[a]	A Study Investigating the Predictive Value of Philadelphia Positive Stem Cell Properties in	250	Jul 2021 (recruiting)

	Newly Diagnosed Patients With Chronic Myeloid in Chronic Phase Receiving Treatment With Imatinib		
NCT01850004[a]	Open-Label Single-Arm Phase 2 Study Evaluating Dasatinib Therapy Discontinuation In Patients With Chronic Phase Chronic Myeloid Leukemia (CP-CML) With Stable Complete Molecular Response (DASFREE)	84	Oct 2021 (ongoing)
NCT02269267	The Life After Stopping Tyrosine Kinase Inhibitors Study (The LAST Study)	173	Dec 2021 (ongoing)
NCT02001818a	Phase II Study of Nilotinib Plus Pegylated Interferon Alfa-2b as First-line Therapy in Chronic Phase Chronic Myelogenous Leukaemia Aiming to Maximize Complete Molecular Response and Major Molecular Response	100	Dec 2021 (recruiting)
NCT03807479[a]	Phase 2 Clinical Trial With Ponatinib as a Second-Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Prior First Line Tyrosine Kinase Inhibitor Treatment	54	Apr 2023 (recruiting)
NCT02917720	Multicenter Prospective Trial After First Unsuccessful Treatment Discontinuation in Chronic Myeloid Leukemia (CML) Estimating the Efficacy of Nilotinib in Inducing the Persistence of Molecular Remission After Stopping TKI a 2nd Time	200	May 2023 (recruiting)
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	136	May 2023 (recruiting)

	Who Have Achieved a Sustained, Deep Molecular Response for at Least 1 Year		
NCT03263572[a]	Phase II Study of the Combination of Blinatumomab and Ponatinib in Patients With Philadelphia Chromosome (Ph)-Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL)	60	Nov 2023 (recruiting)
NCT03817398	Stopping Tyrosine Kinase Inhibitors (TKI) to Assess Treatment-Free Remission (TFR) in Pediatric Chronic Myeloid Leukemia - Chronic Phase (CML-CP)	110	Dec 2023 (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)	600	Feb 2024 (recruiting)
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)	221	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 Individualised, Targeted and Intensified	900	Jun 2025 (recruiting)

	Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients		
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)	320	Jan 2026 (recruiting)
Unpublished			
NCT01343173	Multicenter Trial Estimating the Persistence of Molecular Remission in Chronic Myeloid Leukaemia in Long Term After Stopping Imatinib (STIM 2)	220	May 2017 (completed)
NCT03421626[a]	Clinical Evaluation of the Xpert BCR-ABL Ultra Assay on the GeneXpert Instrument Systems	266	Aug 2018 (completed)

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

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Policy History

Original Effective Date: 07/16/2014
Current Effective Date: 09/14/2020

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.

Next Scheduled Review Date: 08/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Code Type	Code
CPT	0016U, 0040U, 81170, 81206, 81207, 81208, 81401, 81403
HCPCS	No codes
ICD-10 Diagnosis	C91.00-C91.02, C92.10-C92.12

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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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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