BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.85 BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

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Related Policies:

5.21.022- Bosulif (bosutinib)
5.21.030- Iclusig (ponatinib)
5.21.031-Synribo (omacetaxine mepesuccinate)
5.21.063-Sprycel (dasatinib)
5.21.074-Gleevec (imatinib)
5.21.077- Tasigna (nilotinib)

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

Description

Description

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.

OBJECTIVE

The objective of this evidence review is to evaluate whether testing for the *BCR-ABL1* fusion gene improves the net health outcome in individuals with chronic myelogenous leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia.

POLICY STATEMENT

Chronic Myelogenous Leukemia

BCR-ABL1 qualitative testing for the presence of the fusion gene may be considered **medically necessary** for the diagnosis of chronic myeloid leukemia (see Policy Guidelines section).

BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals (see Policy Guidelines section) may be considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of *ABL* kinase domain (KD) single nucleotide variants to assess individuals for tyrosine kinase inhibitor resistance may be considered **medically necessary** when there is an inadequate initial response to treatment or any sign of loss of response (see Policy Guidelines section); and/or when there is a progression of the disease to the accelerated or blast phase.

Evaluation of *ABL* KD single nucleotide variants is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

Acute Lymphoblastic Leukemia

BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines section) may be considered **medically necessary** for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.

Evaluation of *ABL* KD single nucleotide variants to assess individuals for tyrosine kinase inhibitor resistance may be considered **medically necessary** when there is an inadequate initial response to treatment or any sign of loss of response.

Evaluation of *ABL* KD single nucleotide variants is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

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 (see Rationale section).

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 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

Summary of Evidence

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. 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 tyrosine kinase inhibitor (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 tyrosine kinase inhibitors (TKIs) and reported the presence of kinase domain (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 acute lymphoblastic leukemia (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).[20,] 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) 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.[15,] 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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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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2013	New policy	
June 2014	Replace policy	Policy updated with literature review. References 3, 5, 6, 46- 47, 56-57 added. Policy statements added for ALL, medically necessary prior to initiation of treatment, for disease monitoring and to evaluate for TKI resistance. Title also changed to add ALL.
June 2015	Replace policy	Policy updated with literature review. No references added. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through August 23, 2017; reference 41 added; references 3 and 47 updated. Policy statements unchanged.
December 2018	Replace policy	Policy updated with literature review through August 22, 2018; references 23-33 added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through July 25, 2019; references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through September 22, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through August 19, 2021; references added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through August 25, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
December 2023	Replace policy	Policy updated with literature review through August 18, 2023; references added. Policy statements unchanged.