2.04.85	BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia		
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Section:	2.0 Medicine	**Page:**	Page 1 of 33

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 patients 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* kinase domain (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* kinase domain (KD)single nucleotide variants to assess patients 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* kinase domain (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 (i.e., detection of the Philadelphia chromosome) is necessary for accurate diagnosis of chronic myelogenous leukemia (CML). Identification of the Philadelphia chromosome is not necessary to diagnose acute lymphoblastic leukemia (ALL); however, molecular phenotyping is usually performed at the initial assessment (see Determining Baseline RNA Transcript Levels and Subsequent Monitoring subsection).

Distinction between molecular variants (i.e., 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 (see Rationale section).

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

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

Tyrosine Kinase Inhibitor (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 terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to 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

Variant Classification	Definition
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.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

A new code was effective April 1, 2018:

- **0040U**: BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

The following CPT codes are specific for *BCR-ABL1* and *ABL1* testing:

- **81170**: *ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)* (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
- **81206**: BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
- **81207**: BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
- **81208**: BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

CPT code **81401** includes the following test:

- Molecular pathology procedure, Level 2; *ABL1* (*ABL proto-oncogene 1, non-receptor tyrosine kinase*) (e.g., acquired imatinib resistance), T315I variant

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.

Related Policies

- Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the

time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Background
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.[1] 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.[2,] 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 kilodalton (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-ABL1* protein is the same as the KD of the normal *ABL1* protein. However, abnormal *BCR-ABL1* 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.[3,] 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.[4] In the assay, *BCR-ABL1* transcripts are quantified relative to one of three recommended reference genes (e.g., *ABL*) to control for the quality and quantity of RNA and to normalize for potential differences between tests.[4,5,]

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."[6] 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.[8] The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.[8]

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.[6] 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%).[7] 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.[6,8]

Structural studies of the ABL-imatinib complex have resulted in the design of second-generation ABL inhibitors, including dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis), which were initially approved by the U.S. Food and Drug Administration for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of both agents in newly diagnosed chronic-

phase patients have shown that both are superior to imatinib for all outcomes measured after one year of treatment, including complete cytogenetic response (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis.[9,10] Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. The Food and Drug Administration (FDA) has approved third-generation TKIs, ponatinib, and bosutinib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI is indicated. Bosutinib is indicated for Ph-positive CML with resistance or intolerance to prior therapy.

For patients with increasing levels of *BCR-ABL1* transcripts, there is no strong evidence to recommend specific treatment; possibilities include continuation of therapy with dasatinib or nilotinib at the same dose, or imatinib dose escalation from 400 to 800 mg daily, as tolerated, or therapy change to an alternative second-generation TKI.[6]

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.[8] (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.) [11] The degree of resistance depends on the position of the variant within the KD (i.e., active site) of the protein. Some variants are associated with moderate resistance and are responsive to higher doses of TKIs, while other variants may not be clinically significant. Two variants, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance.

The presence of *ABL* SNVs is associated with treatment failure. A large number of variants have been detected, but extensive analysis of trial data with low-sensitivity variant detection methods has identified a small number of variants consistently associated with treatment failure with specific TKIs; guidelines recommend testing for information on these specific variants to aid in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced. Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.

Unlike imatinib, fewer variants are associated with resistance to dasatinib or nilotinib.[12,13] For example, Guilhot et al (2007)[14] and Cortes et al (2007)[15] 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.[11,14] 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.[16] 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.[8] 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.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Laboratory tests to detect the *BCR-ABL1* fusion gene are used to identify chronic myelogenous leukemia (CML) and Philadelphia (Ph) chromosome-positive acute lymphoblastic leukemia (ALL) and have different clinical uses. Briefly, they are as follows:

1. Diagnosis: patients who do not have the *BCR-AB1L* fusion gene by definition do not have CML. In contrast, identification of the *BCR-ABL1* fusion gene is necessary, although not sufficient, for diagnosis. Relevant test technologies are cytogenetics (karyotyping; recommended) or fluorescence in situ hybridization (acceptable in the absence of sufficient sample for karyotyping).
2. Monitoring *BCR-ABL1* RNA transcripts for residual disease during treatment or disease remission; relevant, standardized test technology is quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Note that a baseline measurement after confirmation of a CML diagnosis and before treatment begins is strongly recommended.
3. Identification and monitoring of variants for drug resistance at response failure or disease progression; various test technologies are in use (not standardized) including reverse transcription-polymerase chain reaction(RT-PCR) and Sanger sequencing.

Diagnosis and Pretreatment Workup of Chronic Myelogenous Leukemia

Clinical Context and Test Purpose

The purpose of the *BCR-ABL1* fusion gene qualitative testing in individuals with suspected CML is to inform diagnosis and establish a baseline for monitoring treatment.

The question addressed in this evidence review is: Does the use of qualitative testing for *BCR-ABL1* improve the net health outcome in individuals with suspected CML?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with suspected CML.

Interventions

The test being considered is the*BCR-ABL1* fusion gene qualitative testing.

Comparators

The following practices are currently being used to diagnose CML: clinical and cytogenetic methods.

Outcomes

The general outcome of interest is test validity. Follow-up over years is of interest to monitor outcomes.

Study Selection Criteria

For the evaluation of the clinical validity of the *BCR-ABL1* fusion gene qualitative testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Validation Studies
While the diagnosis of CML is based on the presence of characteristic cellular abnormalities in bone marrow, the presence of the Ph chromosome and/or confirmation of the BCR-ABL1 fusion gene is essential. The initial evaluation of chronic phase CML should include bone marrow cytogenetics, not only to detect the Ph chromosome but also to detect other possible chromosomal abnormalities.[17,] If bone marrow is not available, fluorescence in situ hybridization analysis with dual probes for BCR and ABL genes or q RT-PCR can provide qualitative confirmation of the fusion gene and its type.[17,]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Diagnosis and Pretreatment Workup of CML
The evidence on diagnosis and pretreatment workup in patients with CML includes validation studies. The sensitivity of testing *BCR-ABL* transcript levels with RT-PCR is high compared with conventional cytogenetics. Baseline measurement of *BCR-ABL* transcript levels is recommended as part of the initial evaluation, confirming the fusion gene, ensuring that it is detectable (rare variants requiring nonstandard probes may occur), and providing a baseline for monitoring response to treatment.

Monitoring Treatment Response and CML Remission
Clinical Context and Test Purpose
The purpose of *BCR-ABL1* quantitative testing at appropriate intervals in patients diagnosed with CML is to monitor treatment response and remission.

The question addressed in this evidence review is: Does the use of quantitative testing of *BCR-ABL1* improve the net health outcome in individuals with CML?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals diagnosed with CML.

Interventions
The test being considered is *BCR-ABL1* quantitative testing at appropriate intervals.

The qRT-PCR measurement of *BCR-ABL1* RNA transcript levels is the method of choice for assessing response to treatment because of the high sensitivity of the method and strong correlation with outcomes.[6,] Compared with conventional cytogenetics, qRT-PCR is more than 3 logs more sensitive[18,] and can detect 1 CML cell in the background of 100,000 or more normal cells. The qRT-PCR testing can be conducted on peripheral blood, eliminating the need for bone marrow sampling. The goal of treatment is a complete molecular response (CMR), which has variable definitions based on the assay. However, only a small minority of patients achieve CMR on imatinib.[19,] More often, patients achieve a major molecular response (MMR), which may be defined as a *BCR-ABL1* transcription level of 0.01% or less on the International Scale or a 3-log or more reduction in BCR-ABL1 mRNA from the standardized baseline.

Comparators
The following practice is currently being used to diagnose CML: cytogenetics.

Outcomes
The general outcomes of interest are disease-specific survival, test validity, and change in disease status. Follow-up over years is of interest to monitor outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the *BCR-ABL1* qualitative testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Several studies were excluded from the evaluation of the clinical validity of the xxx test because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinical Studies
Systematic Reviews
Campiotti et al (2017) conducted a systematic review reporting on the safety of imatinib discontinuation in patients who had previously achieved an undetectable BCR-ABL transcript level.[20,] Characteristics and results of the meta-analysis are reported in Tables 3-4.

Table 3. SR & M-A Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration, mo
Campiotti et al (2017)[20,]	2007-2015	15	Individuals with CML who discontinued TKI therapy. Studies reporting clinical outcomes.	509 (11-108)	Prospective cohort studies Retrospective cohort studies	23 (IQR: 18-32)

CML: chronic myelogenous leukemia; IQR: interquartile range; M-A: meta-analysis; SR: systematic review; TKI: tyrosine kinase inhibitor.
[1] Key eligibility criteria.

Table 4. SR & M-A Results

Study	Overall Mean Molecular Relapse Rate	6-mo Mean Molecular Relapse Rate	Overall Survival at 2 y	Disease Progression
Campiotti et al (2017)[20,]				
Total N	509	509	509	509
Pooled effect (95% CI)	51 (44-58)	41 (32-51)	100% (NR)	0.8 (0.2-1.8)
I^2	55	78	NR	0
Range of N	11-108	11-108	11-108	11-108
Range of effect sizes	32-83%	NR	100%	0-1

CI: confidence interval; M-A: meta-analysis; NR: not reported; SR: systematic review.

Nonrandomized Studies

Results from the International Randomized Study of Interferon vs STI571 trial, reported by Druker et al (2006), showed that patients who had a CMR or MMR had a negligible risk of disease progression at 1 year, and a significantly lower risk of disease progression at 5 years than patients who had neither.[21,] At eight-year follow-up, none of the patients who achieved an MMR at one year progressed to the accelerated phase of disease or to a blast crisis. The similar near absence of progression in patients who achieved an MMR has been reported in registration studies of nilotinib and dasatinib.[9,10,19,] Impacts of MMR level monitoring via in-house assays vs PCR kits have been explored elsewhere and have reported identical molecular responses in 98% of samples.[22,]

Several studies have used these tests to guide discontinuation of select tyrosine kinase inhibitors (TKIs) in CML patients who have achieved an appropriate molecular response and to monitor treatment-free remission.[23-33,] The largest of these studies, the European Stop Tyrosine Kinase Inhibitor Study (EURO-SKI) trial, reported by Saussele et al (2018), evaluated discontinuation of TKIs in 755 patients with CML who had been treated with TKIs for more than 3 years and had achieved a molecular response graded as MR4 (BCR-ABL1 transcription level of 0.01% or less on the International Scale [IS]) for at least 1 year.[34,] Molecular response was assessed monthly for the first six months, every six weeks for the remainder of the year, and then every three months for at least three years. The trigger to resume treatment with TKIs was loss of MMR. Treatment-free remission rate was 50% at 2 years (95% CI 46-54); loss of MMR despite restarting TKIs was seen in 2 patients. Similar findings were reported by Ross et al (2019) in recent updates of the Nilotinib Treatment-free Remission Study in CML Patients (ENESTfreedom) Study, a large single-arm phase 2 study, which evaluated discontinuation of first-line treatment with nilotinib in the 190 CML patients who had been treated with nilotinib for more than 2 years and achieved sustained deep molecular response.[35,]The predictive relationship between early molecular response at 3-months and eventual achievement of deep molecular response with imatinib or nilotinib treatment was explored by Wang et al (2019) in 206 patients with chronic-phase CML.[36,] The predictive value of the 3-month molecular response was further supported by Berdeja et al (2019) in the Rates of Deep Molecular Response by Digital and Conventional PCR with Frontline Nilotinib in Newly Diagnose CML (ENESTnext) study, which demonstrated the feasibility of further treatment monitoring at BCR-ABL1 transcript levels below 0.001% on the IS via digital PCR.[37,] Characteristics, results, and limitations of these studies are highlighted in Tables 5-8.

Table 5. Summary of Key Nonrandomized Trials

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Saussele et al (2018); EURO-SKI[34],	Prospective	EU	2012-2018	Patients aged 18 years and older with chronic phase CML that had received any TKI for at least 3 years and achieved an MMR	Patient data (N=755) was further analyzed in learning sample (N=448) or validation sample (N=195) to guide definition of conditions for TKI discontinuation.	27 (IQR: 21-34)
Ross et al (2019); ENESTFreedom[35],	Prospective	U.S., EU, Other	2013-2016	Patients aged 18 years and older with Ph+, chronic phase CML with at least 2 years of frontline nilotinib therapy and MR4.5	Patients treated on nilotinib and followed for 96 weeks for treatment-free remission (N=190).	20 (Range: 2-33)
Wang et al (2019)[36],	Retrospective	China	2010-2018	Patients with chronic-phase CML that were treated with a TKI for at least one year, with molecular response testing at 3- and 6-mo	Patients were allocated to treatment with first-line imatinib or nilotinib based on criteria established by ELN. Molecular response was defined per the international Scale as: • MR4.0: 0.0032% < BCR-ABL^{IS}< 0.01% • MR4.5: 0.001% < BCR-ABL^{IS} < 0.0032% • MR5.0: BCR-ABL^{IS}≤ 0.001% DMR was defined as ≥ MR4.0. The ELN-defined EMR indicative of positive response to TKI treatment are ≤10% at 3-mo and <1% at 6-mo.	27 (IQR: 16-50)
Berdeja et al (2019); ENESTnext[37],	Prospective	US	2010-2019	Adults diagnosed with Ph+ CML in chronic-phase ≤ 6-months prior to study entry; Patients with documented T315I mutation were excluded.	Patients were treated with nilotinib 300 mg twice daily. Dose adjustments were permitted per ELN guidelines. Molecular response was monitored with qRT-PCR monthly for the first 3 months, and every 3 months thereafter. Patients with confirmed MR4.5 (0.001% < BCR-ABL^{IS} < 0.0032%) were further assessed via digital PCR.	26 (Range: <1-49)

CML: chronic myelogenous leukemia; DMR: deep molecular response; ELN: European LeukemiaNet; EMR: early molecular response; IS: international standard; IQR: interquartile range; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; TKI: tyrosine kinase inhibitor; MMR: major molecular response; MR: molecular response; Ph+: Philadelphia chromosome-positive.

Table 6. Summary of Key Nonrandomized Trial Results

Study; Trial	All Patients	MMR Duration at least 3.1 y	Imatinib Treatment Duration at least 5.8 y
Saussele et al (2018); EURO-SKI[34],	755	276	138
Treatment-Free Survival at 6 mo, % (95% CI)	60 (56-63)	NR	63 (57-69)
Loss of MMR after TKI Discontinuation, n (%)	371 (49)	NR	NR
Loss of MMR Despite Restarting TKI, n (%)	2 (<1)	NR	NR
Probability of Maintaining MMR, OR (95% CI)	1.13 (1.04-1.23)	1.97 (1.29-3.00)	2.41 (1.58-3.67)
P value	0.0032	0.0029	0.00090
Ross et al (2019); ENESTFreedom[35],	190	---	---
Week 96 Treatment-Free Remission, % (95% CI)	48.9 (41.6-56.3)	---	---
Week 96 Treatment-Free Survival, % (95% CI)	50.9 (43.6-57.8)	---	---
Wang et al (2019)[36],	EMR at 3-mo		EMR at 6-mo
Total N	162	Total N	164
EMR, overall, n (%)	112 (69.1)	EMR, overall, n (%)	106 (64.6)
EMR with imatinib, n (%)	84 (63.6)	EMR with imatinib, n (%)	59.9
EMR with nilotinib, n (%)	28 (93.3)	EMR with nilotinib, n (%)	88.9
P value (nilotinib vs imatinib EMR)	0.001	P value (nilotinib vs imatinib EMR)	0.004
BCR-ABL^{IS} < 1% with imitinib at 3-mo, %	21.2	BCR-ABL^{IS} < 0.1% with imitinib at 6-mo, %	24.1
BCR-ABL^{IS} < 1% with nilotinib at 3-mo, %	60.0	BCR-ABL^{IS} < 0.1% with nilotinib at 6-mo, %	40.7
P value (nilotinib vs imatinib BCR-ABL^{IS} < 1% at 3-mo)	<0.001	P value (nilotinib vs imatinib BCR-ABL^{IS} < 1% at 3-mo)	0.074
Patients with EMR that achieved MR4.0 by 48 mo, % (95% CI)	62.2 (47.4-77.0)	---	---
Patients without EMR that achieved MR4.0 by 48 mo, % (95% CI)	18.3 (6.4-46)	---	---
Odds of achieving DMR with 1% < BCR-ABL^{IS}≤10% vs BCR-ABL^{IS}≤1%, HR (95% CI) P value	0.285 (0.109-0.747) 0.011	---	---
Odds of achieving DMR with 1% < BCR-ABL^{IS} > 10% vs BCR-ABL^{IS}≤1%, HR (95% CI) P value	0.095 (0.024-0.377) 0.001	---	---
Berdeja et al (2019); ENESTnext[37],	Endpoint: MMR		Endpoint: MR4.5
Total N	128		128
Cumulative rate to endpoint by 24 mo, n (%)	94 (73.4)		34 (26.6)
Loss of endpoint, n (%)	13 (13.8)		6 (17.6)
Median (range) time to endpoint, mo	5.6 (0.9-18.1)		8.3 (1.9-17.5)
Median (range) duration to endpoint, mo	16.5 (0-21.1)		13.9 (4.6-20.3)
Cumulative rate to endpoint with BCR-ABL1^{IS}≤ 10% at 3-mo, n/N (%)	75/87 (86.2)		28/87 (32.2)
Detection of transcripts in first digital PCR, n/N (%)	---		18/33 (54.5)
Absence of transcripts in final digital PCR, n/N (%)	---		22/33 (66.7)

CI: confidence interval; DMR: deep molecular response; EMR: early molecular response; IS: international stanfard; MMR: major molecular response; MR4.5: (0.001% < BCR-ABL^{IS} < 0.0032%); NR: not reported; OR: odds ratio, PCR: polymerase chain reaction; TKI: tyrosine kinase inhibitor.

Table 7. Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Saussele et al (2018); EURO-SKI[34],					
Ross et al (2019); ENESTFreedom[35],					

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Wang et al (2019)[36]	4. Population age has narrow range.				
Berdeja et al (2019); ENESTnext[37]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study; Trial	Selection[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saussele et al (2018); EURO-SKI[34]	1. Allocation not described.	1. Blinding not described.		1. High loss to follow-up or missing data.		
Ross et al (2019); ERNESTFreedom[35]	1. Allocation not described.	1. Blinding not described.			1. Power calculations not reported.	
Wang et al (2019)[36]	1. Allocation not described.	1. Blinding not described.	1. Not registered.	1. High loss to follow-up or missing data.	1. Power calculations not reported.	
Berdeja et al (2019); ENESTnext[37]	1. Allocation not described.	1. Blinding not described.			1. Power calculations not reported.	3. Confidence intervals and/or p values not reported.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

The degree of molecular response has also been reported to correlate with the risk of progression in patients treated with imatinib.[38] Timing of the molecular response is also important; the degree of molecular response at early time points predicts the likelihood of achieving CMR or MMR and predicts improved rates of progression-free and event-free survival.[39-42] While early and strong molecular response predicts durable long-term remission rates and progression-free survival, studies have not been conclusive that molecular response is predictive of overall survival.[43,44,45]

Based on imatinib follow-up data, it is recommended that, for patients with a complete cytogenetic response, molecular response to treatment be measured every three months

for two years, then every three to six months thereafter.[6,46] Without a complete cytogenetic response, continued monitoring at three-month intervals is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib,[6] and would likely also be applied to bosutinib and ponatinib.

Rising *BCR-ABL1* transcript levels are associated with increased risk of variants and treatment failure.[47-52] However, what constitutes a clinically significant rise to warrant variant testing is not known. Factors affecting the clinically significant change include the variability of the specific assay used by the laboratory and the level of molecular response achieved by the patient. Thresholds used include 2- to 10-fold increases, and increases of 0.5 to 1 log, respectively.[48,53] Because of potential variability in results and lack of agreement across studies for an acceptable threshold, rising transcript levels alone are not viewed as sufficient to trigger variant testing or changes in treatment.[54]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Monitoring Treatment Response and CML Remission
The qRT-PCR measurement of *BCR-ABL1* RNA transcript levels is the method of choice for monitoring CML during treatment and in disease remission because of the high sensitivity, strong correlation with outcomes, and ability to sample in peripheral blood.

Identification of *ABL* Kinase Domain Single Nucleotide Variants to Assess TKI Resistance in CML
Clinical Context and Test Purpose
The purpose of the evaluation for *ABL* kinase domain (KD) single nucleotide variants (SNVs) in patients diagnosed with CML and inadequate initial response, loss of response, and/or disease progression is to assess for TKI resistance.

The question addressed in this evidence review is: Does evaluation for *ABL* KD SNVs improve the net health outcome in individuals with CML and inadequate initial response, loss of response, and/or disease progression?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals diagnosed with CML and inadequate initial response, loss of response, and/or disease progression.

Interventions
The test being considered is testing for *ABL*KD SNVs to assess for TKI resistance.

Screening for *BCR-ABL1* KD SNVs in chronic phase CML is recommended for patients with (1) inadequate initial response to TKI treatment, (2) evidence of loss of response, or (3) progression

to accelerated or blast phase CML.[7] Testing for KD SNVs, in the setting of potential treatment failure, may help to select from among other TKI treatments or allogeneic cell transplantation.

Comparators
The following practice is currently being used to assess TKI resistance among patients with an inadequate initial response, loss of response, and/or disease progression: standard workup without genetic testing.

Outcomes
The general outcomes of interest are disease-specific survival, test validity, and medication use. Follow-up over years is of interest to monitor outcomes.

Study Selection Criteria
For the evaluation of clinical validity of the *ABL*KD SNV testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Clinical Studies
The Agency for Healthcare Research and Quality published a systematic review, conducted by Terasawa et al (2010), who assessed *BCR-ABL1* pharmacogenetic testing for TKIs in CML.[55,] Reviewers concluded that the presence of any *BCR-ABL1* variant did not predict differential response to TKI therapy, although the presence of the T315I variant uniformly predicts TKI failure. Reviewers were strongly criticized by respected pathology organizations for insufficient attention to several issues. Importantly, they grouped studies that used KD SNV screening methods with those that used targeted methods, and grouped studies that used variant detection technologies with very different sensitivities.

KD SNVs and Treatment Outcomes
Xue et al (2018) reported on health outcomes in 219 CML patients assessed for additional chromosomal abnormalities or BCR-ABL KD mutations.[56,] Characteristics and results of the study are reported in Tables 9-10. KD mutations were found to have a significant impact on disease

progression compared to additional chromosomal abnormalities . Limitations of the study are reported in Tables 11-12.

Table 9. Summary of Key Nonrandomized Trials

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Xue et al (2018)[56,]	Retrospective	China	2010-2017	Patients with Ph+ and/or BCR-ABL1 positive CML	Cytogenetic karyotype analysis for chromosomal abnormalities and nested PCR for sequencing of BCR-ABL1 KD.	27 (IQR: 21-34)

CML: chronic myelogenous leukemia; IQR: interquartile range; PCR: polymerase chain reaction; Ph+: Philadelphia chromosome-positive.

Table 10. Summary of Key Nonrandomized Trial Results

Study	Presence of ACAs	Presence of KD Mutations in Imatinib-Resistant Patients	Patients w/o ACAs or KD Mutations	Patients w/ ACAs and/or KD Mutations
Xue et al (2018); Total N[56,]	219	53	219	219
Incidence, n (%)	24 (11%)	13 (24.5%) Y253H: 3 (23.07%) F359V: 2 (15.38%) T315I: 2 (15.38%) F317L, L298V, M351T, E255K, E459K, M458I, A337T, V299L, M244V: 1 (7.69%) each	186 (85%)	33 (15%)
Incidence of CML Progression, n (%)	4/20 (20%)	5/9 (55.6%)	2/143 (1.4%)	12/22 (54.5%)
P-value	0.046		<0.001	

ACAs: additional chromosomal abnormalities; CML: chronic myelogenous leukemia; KD: kinase domain.

Table 11. Relevance Limitations

Study; trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of follow-up[e]
Xue et al (2018)[56,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study; Trial	Selection[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Xue et al (2018)[56,]	1. Allocation not described.	1. Blinding not described.	1. Not registered.		1. Power calculations not reported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Branford et al (2009) previously summarized the available evidence on KD SNVs detected after imatinib treatment failure, and subsequent treatment success or failure with dasatinib or nilotinib.[57,] Studies referenced used direct Sanger sequencing, with or without denaturing high-performance liquid chromatography screening, to identify variants at low sensitivity. The authors surveyed variants detected in patients at imatinib failure at their own institution and compared results with a collation of variants derived from the literature. For both, the T315I variant was most common; although about 100 variants have been reported, the 7 most common (at residues T315, Y253, E255, M351, G250, F359, and H396) accounted for 60% to 66% of all variants in both surveys. Detection of the T315I variant at imatinib failure is associated with lack of subsequent response to high-dose imatinib or to dasatinib or nilotinib. For these patients, allogeneic cell transplantation was the only available treatment until the approval of new agents (e.g., ponatinib).[58,] Most common, however, does not necessarily correspond to clinically significant. Based on the available clinical studies, most imatinib-resistant variants remain sensitive to dasatinib and nilotinib. However, preexisting or emerging variants T315A, F317L, F317I, F317V, F317C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging variants Y253H, E255K, E255V, and F359V, and F359C have been reported to have decreased clinical efficacy with nilotinib treatment following imatinib failure. In the Branford survey, 42% of patients tested had T315Ior one of the dasatinib- or nilotinib-resistant variants.[57,] As a result, guidelines recommend variant analysis only at treatment failure, and use of the T315I variant and the identified dasatinib- and nilotinib-resistant variants to select a subsequent treatment.[6,54,] Absent any of these actionable variants, various treatment options are available. Note that these data were obtained from studies of patients all initially treated with imatinib.

ABL KD SNV analysis is recommended if there is inadequate initial response (failure to achieve complete hematologic response at 3 months, only minor cytologic response at 6 months, or major [rather than complete] cytogenetic response at 12 months) or any sign of loss of response (defined as hematologic relapse, cytogenetic relapse, or 1-log increase in *BCR-ABL1* transcript ratio and therefore loss of MMR). Variant testing is also recommended for progression to accelerated or blast phase CML. Treatment recommendations based on the variant(s) are shown in Table 3.

Because only a small number of variants have been recommended as clinically actionable, targeted assays may also be used to screen for the presence of actionable variants at treatment failure. Quantitative, targeted assays may also be used to monitor levels of already identified clinically significant variants after starting a new therapy because of initial treatment failure. Targeted assays use different technologies that can be very sensitive and pick up mutated cell clones at very low frequencies in the overall malignant population. Banked samples from completed trials have been studied with high-sensitivity assays to determine if monitoring treatment can detect low-level variants that predict treatment failure well in advance of clinical indications. Some results have been positive, but not all variants detected in advance predict treatment failure; more study is recommended before these assays are used for monitoring in advance of treatment failure.[54,57,] A direct correlation between low-sensitivity and high-sensitivity assays and a limited correlation with clinical outcomes support recommendations of sequencing, with or without denaturing high-performance liquid chromatography screening, for identification of variants.[59,]Although high-sensitivity assays identified more variants than did sequencing, the clinical impact of identifying additional variants is uncertain.

Variants other than point mutations can be detected in the *BCR-ABL1* gene, including alternate splicing, insertions, deletions, and/or duplications. The clinical significance of such altered transcripts is unclear, and reporting such variants is not recommended.[8,60,]

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Identification of *ABL* KD SNVs to Assess TKI Resistance in CML
Studies have evaluated pharmacogenetics testing for TKIs and have shown a correlation between certain types of variants and treatment response. Testing for SNVs, in the setting of potential treatment failure, may help to select from among other TKI treatments or allogeneic cell transplantation.

Monitoring Ph-Positive ALL
Clinical Context and Test Purpose
The purpose of *BCR-ABL1* quantitative testing at baseline before and during treatment in patients with a diagnosis of Ph-positive ALL is to monitor treatment response and remission.

The question addressed in this evidence review is: Does quantitative testing of *BCR-ABL1* improve the net health outcome in individuals with Ph-positive ALL?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with a diagnosis of Ph-positive ALL.

Interventions
The test being considered is *BCR-ABL1* quantitative testing at baseline before and during treatment to monitor treatment response and remission.

Comparators
The following test is currently being used to monitor treatment response and remission in those diagnosed with Ph-positive ALL: cytogenetics.

Outcomes
The general outcomes of interest are disease-specific survival, test validity, and change in disease status. Follow-up over years is of interest to monitor outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the *BCR-ABL1* quantitative testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Diagnosis and Pretreatment Workup
The diagnosis of ALL is made by demonstrating 20% or greater bone marrow lymphoblasts; demonstration of the *BCR-ABL* fusion gene is not essential. However, identification of specific molecular subtypes is recommended at the time of diagnosis for optimal risk evaluation and treatment planning. The initial evaluation of ALL patients should include bone marrow sample for RT-PCR for *BCR-ABL* to establish the presence or absence of *BCR-ABL*, as well as baseline transcript quantification.[61,]

Monitoring for Residual Disease During Treatment and Disease Remission
Despite significantly higher complete response rates with TKIs in Ph-positive ALL, the response is typically short-lived, and relapses are common.[61,] The principal aim of therapy after remission is to eradicate the minimal residual disease (MRD), which is the prime cause of relapse.[61,]

Studies in children and adults with ALL have demonstrated a strong correlation between MRD and risk for relapse, as well as the prognostic significance of measuring MRD during and after initial induction therapy. A commonly used cutoff to define MRD positivity is 0.01%, with patients who attain an MRD less than 0.01% early during therapy having high odds of remaining in continuous complete response with contemporary postremission therapy.[62,]

A study of 3184 B-cell ALL children by Conter et al (2000) enrolled in the The Associazione Italiana di Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Münster Acute Lymphoblastic Leukemia(AIEOP-BFM ALL 2000) treatment protocol demonstrated that a risk classification algorithm based on MRD measurements using PCR on days 33 and 78 of treatment was superior to that of other risk stratification criteria based on white blood cell count, age, early response to prednisone, and genetic subtype.[63,] Characteristics and results of the study are presented in Tables 13 and 14. Study limitations are reported in Tables 15 and 16.

Table 13. Summary of Key Nonrandomized Trials

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Conter et al (2010); AIEOP-BFM ALL 2000[63,]	Prospective	EU	2004-2006	Patients aged between 1 and 18 y with Ph+ subtype ALL enrolled in the AIEOP-BFM ALL 2000 study	Risk stratification for EFS by MRD and monitoring of MRD via qRT-PCR analysis (N= 3184 Ph-; 79 Ph+). Patients were stratified to MRD standard, intermediate, and high-risk groups.	NR

ALL: acute lymphoblastic leukemia; EFS: event-free survival; MRD: minimal residual disease; NR: no response; Ph+: Philadelphia chromosome positive; qRT-PCR: quantitative reverse-transcription polymerase chain reaction.

Table 14. Summary of Key Nonrandomized Trial Results

Study	EFS in Ph+ ALL			EFS in Ph- ALL		
Conter et al (2010); AIEOP-BFM ALL 2000; Total N[63,]	54			3184		
MRD Risk Stratification	SR	IR	HR	SR	IR	HR
Incidence, Patients (%)	8	24	22	37	130	70
Incidence, Events (%)	2	8	18	2	25	36
EFS, % (SE)[1]	72.9 (16.5)	68.7 (9.9)	31.8 (9.9)	5-yr: 92.2 (5.6) 7-yr: 92.2 (5.6)	5-yr: 77.4 (4.3) 7-yr: 77.4 (4.3)	5-yr: 47.3 (6.4) 7-yr: 39.4 (9)
P-value	<0.001			<0.001		

ALL: acute lymphoblastic leukemia; EFS: event-free survival; IR: intermediate-risk; HR: high-risk; MRD: minimal residual disease; Ph-: Philadelphia chromosome-negative; Ph+: Philadelphia chromosome-positive; SE: standard error; SR: standard risk.

[1] EFS is reported at 4-yr for Ph+ ALL and at both 5-yr and 7-yr for Ph- ALL.

Table 15. Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Conter et al (2010)[63,]	4. Study population restricted to pediatric patients.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 16. Study Design and Conduct Limitations

Study; Trial	Selection[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Conter et al (2010)[63,]	3. Allocation concealment unclear.	1. Blinding not described.			1. Power calculations not reported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

MRD is also a strong prognostic factor for children and adolescents with first-relapse ALL who achieve a second remission.[62,] Patients with an MRD of 0.01% or more are eligible for allogeneic hematopoietic cell transplantation, whereas achievement of MRD negativity may be an indication for chemotherapy.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Monitoring Ph-Positive ALL
Evidence on the diagnosis, pretreatment workup, and monitoring for residual disease during treatment and disease progression in patients with Ph-positive ALL includes a prospective cohort study and case series. These studies have shown high sensitivity for *BCR-ABL1* quantitative testing and a strong correlation with outcomes, including the risk of disease progression. This may stratify patients to different treatment options.

Identification of ABL KD SNVs Associated With TKI Resistance in Ph-Positive ALL
Clinical Context and Test Purpose
The purpose of testing for *ABL* KD SNVs in patients with Ph-positive ALL and signs of treatment failure or disease progression is to assess for TKI resistance.

The question addressed in this evidence review is: Does testing of *ABL* KD SNVs improves the net health outcome in individuals with Ph-positive ALL?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with Ph-positive ALL and signs of treatment failure or disease progression.

Interventions
The testing being considered is an evaluation for *ABL* KD SNVs to assess for TKI resistance.

Comparators
The following practice is currently being used to monitor patients with Ph-positive ALL and signs of treatment failure or disease progression: standard workup without genetic testing.

Outcomes
The general outcomes of interest are test validity and medication use. Follow-up over years is of interest to monitor outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the *ABL*KD SNV testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Clinical Studies
Resistance to TKIs in ALL is less well studied. Detection of variants was used to evaluate sensitivity to second- or third-generation TKI in case series by Soverini et al (2016).[64,] Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or competition of other coexisting subclones.[61,] In patients with ALL receiving a TKI, a rise in the *BCR-ABL* protein level while in hematologic complete response or clinical relapse warrants variant analysis.[61,]

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Identification of ABL SNVs Associated With TKI Resistance in Ph-Positive ALL
Evidence on the identification of *ABL* SNVs associated with TKI resistance in patients with Ph-positive ALL includes case series. These 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.

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. The relevant outcome is test validity. The sensitivity of testing with RT-PCR is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive *BCR-ABL1* fusion gene quantitative testing at appropriate intervals for monitoring treatment response and remission, the evidence includes a 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 SNVs to assess for TKI resistance, the evidence includes a systematic review and retrospective cohort study case. 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 SNVs detected at imatinib failure. These studies have shown a correlation between certain types of variants, treatment response, and the selection of subsequent treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of 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 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 Ph-positive ALL and signs of treatment failure or disease progression who receive an evaluation for *ABL1* KD SNVs to assess for TKI resistance, the evidence includes case series. 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 17).[6,] 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 17. 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.[65,] Treatment options based on BCR-ABL Mutation Profile are shown in Table 18. The tyrosine kinase inhibitor treatment options for acute lymphoblastic leukemia are the same as for chronic myelogenous leukemia.

Table 18. 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 19.

Table 19. 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 Leukemia (CML) in Early Chronic Phase: a Phase II Exploratory, Multicenter Study	70	Dec 2018 (ongoing)
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-ABL	400	Jun 2020 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Currently Being Treated With First or Subsequent TKI Therapy in the UK, Ireland, or France Using Next-Generation Sequencing		
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 Newly Diagnosed Patients With Chronic Myeloid in Chronic Phase Receiving Treatment With Imatinib	250	Jul 2021 (recruiting)
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 Who Have Achieved a Sustained, Deep Molecular Response for at Least 1 Year	136	May 2023 (recruiting)
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	221	Feb 2025 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Minimal Residual Disease (MRD) Status on First Line Nilotinib Treatment (ENESTFreedom)		
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 Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients	900	Jun 2025 (recruiting)
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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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- Physician order for genetic test
- Name and description of genetic test
- Name of laboratory that performed the test
- Any available evidence supporting the clinical validity/utility of the specific test
- CPT codes billed for the particular genetic test
- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	0040U	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	81170	*ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)* (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

Type	Code	Description
	81207	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
	81208	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
	81401	Molecular pathology procedure, Level 2
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
06/30/2015	BCBSA Medical Policy adoption	Medical Policy Committee
02/01/2016	Coding update	Administrative Review
06/01/2016	Policy revision without position change	Medical Policy Committee
09/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2017	Policy revision without position change	Medical Policy Committee
05/01/2018	Coding update	Administrative Review
12/01/2018	Policy revision without position change	Medical Policy Committee
12/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.