Medical Policy

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

Description/Background

MYELOGENOUS LEUKEMIA AND LYMPHOBLASTIC LEUKEMIA

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias.[1] The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase.[2] 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, very high or very low platelet counts.[3-6] From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow.

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

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs.[7] ALL is the most common childhood tumor, and represents 75% to 80% of acute leukemias in children.[8] ALL represents only 20% of all leukemias in the adult population.[9] The median age at diagnosis is 17 years; more than 50% of patients are diagnosed at younger than 20 years of age.[10] Current survival

rates for patients with ALL have improved dramatically over the past several decades, primarily in children, largely due to advances in the understanding of the molecular genetics of the disease, the incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of about 80%. The long-term prognosis among adults is poor, with cure rates of 30% to 40%, 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 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.[11] In ALL, the Ph is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is generally associated with acute lymphoblastic leukemia, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain of the *BCR-ABL* protein is the same as the kinase domain of the normal ABL protein. However, the abnormal *BCR-ABL* protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Diagnosis

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

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

Standardization of *BCR-ABL1* Quantitative Transcript Testing

A substantial effort has been made to standardize the BCR-ABL1quantitative reverse transcription-polymerase chain reaction qRT-PCR 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.[12] 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.[13,14]

Treatment and Response and Minimal Residual Disease

Before initiation of therapy of 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 that the degree of molecular response correlates with risk of progression. In addition, 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 (PCR)–based methods and International Standards for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec), a tyrosine kinase inhibitor (TKI) was originally developed to specifically 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."[15] As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML. More recent studies have demonstrated that treatment-free remission (i.e., discontinuation of certain TKIs) is safe and feasible in select patients with a stable molecular response of sufficient depth.

With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60% to 80% of patients achieving CR, significantly lower than that achieved in Ph-negative ALL. The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.[16]

Treatment response in Ph-positive ALL is evaluated initially by the hematologic and morphologic response (normalization of peripheral blood counts with trilineage hematopoiesis, <5% bone marrow blasts, and absence of circulating blasts and extramedullary disease), then by flow cytometry or molecular pathology.[15] It is well established that most "good responders" who are considered to be in morphologic remission may still have considerable levels of leukemia cells, referred to as minimal (or measurable) residual disease (MRD). Among children with ALL who achieve a complete response by morphologic evaluation after induction therapy, 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (sensitivity of MRD detection, 0.01%) or next-generation sequencing or polymerase chain reaction-based molecular analyses (e.g., Ig and T-cell receptor gene rearrangements, sequencing of fusion genes, or analysis of BCR-ABL transcripts), the latter of which are the most sensitive methods of monitoring treatment response (sensitivity,0.0001%).[7]

Treatment Resistance

Imatinib treatment usually does not completely eradicate malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. Also, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. The molecular basis for resistance is explained in the following section. When the initial response to treatment with imatinib or another front-line TKI is inadequate or there is a loss of response, resistance variant analysis is recommended to support a diagnosis of resistance (based on hematologic, cytogenetic, and/or molecular relapse) and to guide the choice of alternative doses or treatments[15,].[16,]

Structural studies of the ABL -imatinib complex have resulted in the design of newer -generation ABL inhibitors, including bosutinib (Bosulif; Pfizer), dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis), which were initially approved by the U.S. Food and Drug Administration (FDA) for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of these agents in newly diagnosed chronic-phase patients have demonstrated superiority to imatinib for outcomes including complete cytogenetic response , major molecular response, time to remission, and/or rates of progression to accelerated phase or blast crisis, leading to their approval for front-line chronic phase use.[17,18,19,] The FDA has also approved the third-generation TKI ponatinib and the allosteric ABL1 inhibitor asciminib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI is indicated, while asciminib is indicated for the treatment of chronic-phase CML in patients with T315I or who have received prior treatment with ≥2 TKIs.

There is no strong evidence to recommend specific treatment changes on the sole basis of rising *BCR-ABL1* transcripts detected by quantitative polymerase chain reaction.[20]

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.[16] New *BCR-ABL* SNVs also occur in 80% to 90% of cases of ALL in relapse after TKI treatment and in CML blast transformation.[21] 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.[20] The consensus-recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced.[12] Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.

Unlike imatinib, fewer variants are associated with resistance to bosutinib, dasatinib, or nilotinib.[22,23,] For example, Guilhot et al (2007)[24,] and Cortes et al (2007)[25,] studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell *BCR-ABL1* variants. However, neither bosutinib, dasatinib, nor nilotinib are effective against resistant clones with the T315I variant.[21,24,] 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.[26,] 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.[16,] Resistance in ALL to TKIs is less well studied. In patients with ALL receiving a TKI, a rise in the *BCR-ABL* level while in hematologic complete response or clinical relapse warrants variant analysis.

Regulatory Status

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

On February 2019, the QXDx BCR-ABL % IS Kit (Bio-Rad Laboratories) was approved by the FDA through the 510(k) pathway (K181661). This droplet digital PCR (ddPCR) test may be used in patients with diagnosed t(9;22) positive CML, during monitoring of treatment with TKIs, to measure BCR-ABL1 to ABL1 mRNA transcript levels, expressed as a log molecular reduction value from a baseline of 100% on the International Scale (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 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.

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.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The *BCR/ABL1* qualitative and quantitative genotyping tests and *ABL* KD mutation tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The safety and effectiveness of genetic testing for BCR/ABL1 in individuals undergoing evaluation for or diagnosed with chronic myelogenous leukemia (CML) or acute lymphoblastic leukemia (ALL) have been established. It may be considered a useful tool when indicated

Inclusionary and Exclusionary Guidelines

Chronic Myelogenous Leukemia
BCR-ABL1 qualitative testing for the presence of the fusion gene is established for the diagnosis of chronic myeloid 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 is established for monitoring of chronic myeloid leukemia treatment response and remission.

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

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 is established for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.

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

Testing
Next-generation sequencing (NGS), with a multiple-gene panel test (e.g., CPT* code 81450, or 81455), may be considered established when used for diagnostic and prognostic purposes or for guidance in the selection of appropriate FDA therapeutic options.

Proprietary Laboratory Analyses (PLA) Testing
A PLA test as an FDA-approved companion diagnostic to determine the appropriate therapeutic drug is considered **established** when the following criteria are met:

- Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section “Indications and Usage”), AND
- The test is an FDA-approved companion diagnostic, AND
- The FDA has **not** identified a non-PLA test (e.g., an FDA companion diagnostic that is billed by a CPT code) for the same therapeutic indication.

FDA-Approved Companion Diagnostic Tests
FDA-approved companion diagnostic tests include:

- Tests which are billed with CPT* codes (most laboratories are able to process these)
- Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in “U.”

Exclusions:
BCR/ABL1 testing and Kinase domain mutation testing is considered investigational for all other indications.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81206	81207	81208	81170	81401	81450
81455	0016U	0040U			

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

The assessment of a genetic test typically focuses on 3 categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes).

Laboratory tests to detect the *BCR-ABL1* detection are associated with 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 (RT-PCR). Note that a baseline measurement after confirmation of 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 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 a diagnosis and establish a baseline for monitoring treatment.

The specific clinical context of each test is described briefly in the following sections. The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with suspected CML.

Interventions
The interventions of interest are various tests that assess the presence of 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.

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 Philadelphia chromosome (Ph) and/or confirmation of the *BCR-ABL1* fusion gene is essential to diagnosis. The initial evaluation of chronic phase CML should include bone marrow cytogenetics, not only to detect the Ph chromosome, but to detect other possible chromosomal abnormalities. If bone marrow is not available, FISH analysis with dual probes for *BCR* and *ABL* genes or qualitative RT-PCR can provide qualitative confirmation of the fusion gene and its type.[27]

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 individuals diagnosed with CML is to monitor treatment response and remission.

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

Populations
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.[20,] Compared with conventional cytogenetics, qRT-PCR is more than 3 logs more sensitive[28,] 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.[29,] More often, patients achieve a major molecular response (MMR), which may be defined as a *BCR-ABL1* transcription level of 0. 1% or less on the International Scale (IS) or a 3-log or more reduction in BCR-ABL1 mRNA from the standardized baseline.[20,] Because of the inherent imprecision of a response defined by undetectable *BCR-ABL1* transcripts, which thereby varies according to the sensitivity of the test used, CMR is no longer used in guidelines, and has instead been replaced with deep molecular response, which is defined by the sensitivity of the test (e.g., *BCR-ABL1* transcripts of 0.01% or less on the IS or a 4-log or greater reduction from the standardized baseline, or transcripts of 0.0032% or less or a 4.5-log or greater reduction 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.

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).

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.[30] Characteristics and results of the meta-analysis are reported in Tables 1-2.

Table 1. SR & M-A Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration, mo
Campiotti et al (2017)[30]	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 2. 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)[30]				
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.[31] 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.[17,18] 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.[18,32]

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.[33,34,35,] 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 IS) for at least 1 year.[36,] Molecular response was assessed monthly for the first 6 months, every 6 weeks for the remainder of the year, and then every 3 months for at least 3 years. The trigger to resume treatment with TKIs was loss of MMR. Treatment-free remission rate was 50% at 2 years (95% confidence interval [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.[37,] 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.[38,] 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 Diagnosed 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.[39,] Discontinuation of therapy with first- or subsequent-line dasatinib was investigated by Shah et al (2020) in the DASFREE trial.[40,] Patients were required to have been treated for a minimum of 2 years and to have achieved dasatinib-induced MR4.5 for at least 1 year prior to study entry. The primary outcome was the rate of treatment-free remission (TFR), defined as the proportion of patients with maintained MMR without restarting treatment, at 1 year post-discontinuation of dasatinib. At 1 year, TFR was 48% (95% CI, 37% to 59%) in all enrolled patients. Multivariate analyses revealed statistically significant associations between 2-year TFR and duration of prior dasatinib therapy (≥median; p =.0051), line of therapy (first-line; p =.0138), and age (>65 years; p =.0012). The final 5-year analysis of DASFREE was published in 2023.[41,] Univariate analysis indicated patients aged ≥65 years (hazard ratio [HR] for age <65 years, 2.744; 95% CI, 1.136 to 6.626), those who had received dasatinib as first-line therapy (HR, 0.393; 95% CI, 0.168 to 0.918), or had received dasatinib for a duration equal to or longer than the median duration (HR, 0.524; 95% CI, 0.277 to 0.990) experienced favorable TFR rates.

Characteristics, results, and limitations of these studies are highlighted in Tables 3-6.

Table 3. Summary of Key Nonrandomized Trials

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Saussele et al (2018); EURO-SKI[36,]	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[37,]	Prospective	US, 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)[38,]	Retrospective	China	2010-2018	Patients with chronic-phase CML that were treated with a TKI for at least 1 year, with molecular response testing at 3- and 6-months	Patients were allocated to treatment with first-line imatinib or nilotinib based on criteria established by ELN. Molecular response was defined per the IS 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-months.	27 (IQR: 16-50)
Berdeja et al (2019); ENESTnext[39,]	Prospective	US	2010-2019	Adults diagnosed with Ph+ CML in chronic-phase ≤ 6-months prior to study entry;	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	26 (Range: <1-49)

				Patients with documented T315I mutation were excluded.	assessed via digital PCR.	
Shah et al (2023); DASFREE[41,][Shah NP, García-Gutiérrez V, Jiméne.... 61(3): 650-659. PMID 31647335]	Prospective	US, EU, Other	2013-2021	Patients aged 18 years and older with chronic phase CML receiving first- or subsequent-line dasatinib therapy for a minimum of 2 years and had confirmed MR4.5 for at least 1 year; Patients were required to have a 1-log reduction in *BCR-ABL1* relative to baseline at 3 months with current dasatinib therapy	Patients discontinued dasatinib and were followed for at least 60 months for treatment-free remission (N=84).	Minimum: 60

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 4. 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[36,]	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	.0032	.0029	.00090
Ross et al (2019); ENESTFreedom[37,]	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)[38,]	**EMR at 3-months**		**EMR at 6-months**
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)	.001	P value (nilotinib vs imatinib EMR)	.004
BCR-ABL^{IS} < 1% with imatinib at 3-mo, %	21.2	BCR-ABL^{IS} < 0.1% with imatinib at 6-months, %	24.1
BCR-ABL^{IS} < 1% with nilotinib at 3-mo, %	60.0	BCR-ABL^{IS} < 0.1% with nilotinib at 6-months, %	40.7
P value (nilotinib vs imatinib BCR-ABL^{IS} < 1% at 3-mo)	<.001	P value (nilotinib vs imatinib BCR-ABL^{IS} < 1% at 3-months)	.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);.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);.001	---	---
Berdeja et al (2019); ENESTnext [39,]	**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)
Shah et al (2023); DASFREE[41,]	Endpoint: TFR at 5 years		Endpoint: PFS
Total N	84		84
Overall Rate, % (95% CI)	44 (33 to 54)		2 y: 99 (96 to 100) 5 y: 99 (NR); no new events reported after 2 y follow-up
First-line Therapy Rate, % (95% CI)	46 (29 to 62)		2 y: 100 (100 to 100) 5 y: NR
Subsequent-Line Therapy Rate, % (95% CI)	42 (28 to 57)		2 y: 98 (93 to 100) 5 y: NR

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

Table 5. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Saussele et al (2018); EURO-SKI[36,]					
Ross et al (2019); ENESTFreedom[37,]					
Wang et al (2019)[38,]	4. Population age has narrow range.				
Berdeja et al (2019); ENESTnext[39,]					
Shah et al (2023); DASFREE[41,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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 6. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saussele et al (2018); EURO-SKI[36,]	1. Allocation not described.	1. Blinding not described.		1. High loss to follow-up or missing data.		
Ross et al (2019); ERNESTFreedom[37,]	1. Allocation not described.	1. Blinding not described.			1. Power calculations not reported.	
Wang et al (2019)[38,]	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[39,]	1. Allocation not described.	1. Blinding not described.			1. Power calculations not reported.	3. Confidence intervals and/or p values not reported.
Shah et al (2023); DASFREE[41,]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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 been reported to correlate with the risk of progression in patients treated with imatinib.[42] 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.[42,43,38,39]

The open-label, phase 2 STop IMatinib 2 (STIM2) study utilized droplet digital PCR (ddPCR) to quantify *BCR-ABL1* transcript levels for 175 patients with chronic phase CML and undetectable transcripts by RT-qPCR for at least 2 years prior to imatinib discontinuation.[44] A conversion factor was calculated for ddPCR to apply positive *BCR-ABL1* ratios on the IS. In a multivariate analysis, duration of imatinib therapy (≥74.8 months) and ddPCR (≥ 0.0023% IS) were identified as predictive factors of molecular recurrence, with p =.0366 (HR , 0.635; 95% CI, 0.415 to 0.972) and p =.008 (HR, 0.556; 95% CI, 0.360 to 0.858), respectively. Overall TFR at 12 months was 49% overall compared to 54% in patients negative on ddPCR and those below 0.0023% IS on ddPCR. For patients above 0.0023% IS on ddPCR, TFR was 32%. While the use of ddPCR was investigated as a more sensitive technology compared to qPCR, the authors note that standardizing ddPCR readings on the IS across labs is challenging.[45]

Atallah et al (2021) evaluated molecular recurrence after TKI discontinuation in 171 patients with CML.[46] Monitoring for molecular recurrence (BCR-ABL1 >0.1%) was performed using PCR on the IS scale. Patients were classified as having undetectable (<MR4.5 with adequate ABL1 control amplification; n=143) or detectable (n=28) BCR-ABL1 IS ratio. Molecular recurrence was significantly associated with undetectable BCR-ABL1 transcripts by either ddPCR or RQ-PCR at the time of TKI discontinuation (HR, 3.60; 95% CI, 1.99-6.50) and at 3 months (HR, 5.86; 95% CI, 3.07-11.1).

Haddad et al (2022) evaluated TFR after TKI discontinuation in 199 patients with CML.[47] Monitoring for MMR (BCR-ABL1/ABL1 transcript ratio ≤ 0.1% IS) was determined by quantitative real-time PCR. Failure of TFR was defined as the loss of MMR (QR-PCR >0.1% IS) on a single test and CMR was defined as undetectable transcript levels. At 36 months after TKI discontinuation, 53 patients lost MMR; the estimated 5-year TFR rate was 79%. Estimated 5-year TFR rates were higher with MR4 and MR4.5 at ≥5 years versus MR4 at <5 years (87% vs. 92% vs. 64%, respectively; p<.0001).

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.[48-50]

Based on imatinib follow-up data, it is recommended that for patients with a complete cytogenetic response, molecular response to treatment be measured every 3 months for 2 years, then every 3 to 6 months thereafter.[51,52] Without complete cytogenetic response (CCyR),

continued monitoring at 3-month intervals is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib as well,[15] and will likely also be applied to bosutinib and ponatinib.

Rising *BCR-ABL1* transcript levels are associated with increased risk of mutations and of treatment failure.[53-56] However, the amount of rise that is considered clinically significant for considering mutation testing is not known. Factors affecting the clinically significant change include the variability of the specific assay used by the laboratory, as well as the level of molecular response achieved by the patient. Thresholds used include 2- to 10-fold increases, and increases of 0.5-1 log.[57] 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 mutation testing or changes in treatment.[58]

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 RT-PCR (qRT-PCR) measurement of *BCR-ABL1* RNA transcript levels is the method of choice for assessing response to treatment in CML 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 individuals diagnosed with CML and inadequate initial response, loss of response, and/or disease progression is to assess for TKI resistance.

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

Populations
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.[8] 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 work-up 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

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.[59] 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.[60] Characteristics and results of the study are reported in Tables 7-8. 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 9-10.

Table 7. Summary of Key Nonrandomized Trials

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Xue et al (2018)[60]	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 8. 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)[60]; Total N	219	53	219	219
Incidence, n (%)	24 (11%)	13 (24.5%) Y253H: 3 (23.07%) F359V: 2 (15.38%) T3151: 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 9. Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Xue et al (2018)[60]					

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 10. 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)[60,]	1. Retrospective study	1. Retrospective study	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 much of the available evidence regarding KD SNVs detected at imatinib failure, and subsequent treatment success or failure with dasatinib or nilotinib.[61] Studies referenced used direct Sanger sequencing, with or without DHPLC screening, to identify mutations at low sensitivity. The authors conducted a survey of mutations detected in patients at imatinib failure at their own institution and compared it with a collation of mutations derived from the literature. For both, the *T315I* mutation was most common; although about 100 mutations have been reported, the 7 most common (at residues *T315*, *Y253*, *E255*, *M351*, *G250*, *F359*, and *H396*) accounted for 60% to 66% of all mutations in both surveys. Detection of the *T315I* mutation at imatinib failure is associated with lack of subsequent response to high-dose imatinib, or to dasatinib or nilotinib. For these patients, allogeneic stem cell transplantation remained the only available treatment until the advent of new agents such as ponatinib.[62] Most common, however, does not necessarily correspond to clinically significant. Based on the available clinical studies, most imatinib-resistant mutations remain sensitive to dasatinib and nilotinib. However, preexisting or emerging mutations *T315A*, *F317L/I/V/C*, and *V299L* are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging mutations *Y253H*, *E255K/V*, and *F359V/C* have been reported for decreased clinical efficacy with nilotinib treatment following imatinib failure. In the survey reported by Branford et al, a total of 42% of patients tested had *T315I* or one of these dasatinib- or nilotinib-resistant variants.[61] As a result, guidelines recommend mutation analysis only at treatment failure, and use of the *T315I* mutation and the identified dasatinib- and nilotinib-resistant mutations to select the subsequent treatment.[15,58] In the absence of any of these actionable mutations, various treatment options are available. Note that these data have been obtained from studies in which patients were 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 major molecular response). Mutation testing is also

recommended for progression to accelerated or blast phase CML. Treatment recommendations based on variant(s) are shown in Table 3.

Because only a small number of mutations have been recommended as clinically actionable, targeted assays may also be used to screen for the presence of actionable mutations at treatment failure. Quantitative, targeted assays may also be used to monitor levels of already identified clinically significant mutations after starting a new therapy following initial treatment failure. Targeted assays use different technologies, which can be made very sensitive to 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 mutations that predict treatment failure well in advance of clinical indications. Some results have been positive, not all mutations detected in advance predict treatment failure; more study is recommended before these assays are used for monitoring in advance of treatment failure.[58,61] A direct correlation of low-sensitivity and high-sensitivity assays and a limited correlation with clinical outcomes support recommendations of sequencing, with or without DHPLC screening, for identification of mutations.[63] Although high-sensitivity assays identified more mutations than did sequencing, the clinical impact of the additional variants is uncertain.

Variants other than point variants 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 mutations is not recommended.[16,64]

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
The evidence on identification of ABL SNVs to assess TKI resistance in patients with CML includes a systematic review and case series. These studies have evaluated pharmacogenetics testing for tyrosine kinase inhibitors 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 individuals with a diagnosis of Ph-positive ALL is to monitor treatment response and remission.

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

Populations
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 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.

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.[65]

Monitoring for Residual Disease During Treatment and Disease Remission
Despite significantly higher complete response (CR) rates with the use of tyrosine kinase inhibitors (TKIs) in Ph-positive ALL, the response is typically short-lived and relapses are common. The principal aim of post remission therapy is eradicating minimal residual disease (MRD), which is the prime cause for relapse.[65]

Studies in both 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 MRD less than 0.01% early during therapy having high odds of remaining in continuous CR with contemporary post-remission therapy.[66]

Arunachalam et al (2020) performed a retrospective cohort analysis of 94 patients with Ph-positive ALL.[67] The median age was 33 years (range, 14 to 70 years). Patients were categorized based on MRD good risk or poor risk groups based on BCR-ABL copy number ratio. In the entire cohort, the 5-year OS and event-free survival (EFS) were 45.2% and 35.2%, respectively, and median OS and EFS were 46 months and 28 months, respectively. In multivariate analysis, MRD poor risk stratification was associated with worse OS (HR, 2.9; CI, 1.10 to 7.84) and EFS (HR, 5.4; CI, 2.23 to 13.23).

A study of 3184 B-cell ALL children enrolled in the Associazione Italiana di Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Munster Acute Lymphoblastic Leukemia (AIEOP-BFM ALL 2000) treatment protocol demonstrated that a risk classification algorithm based on MRD measurements by 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.[68] Characteristics and results of the study are presented in Tables 11 and 12. Study limitations are reported in Tables 13 and 14.

Table 11. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Arunachalam et al (2020)[67,]	Retrospective	India	2006-2018	Adult, adolescent, and young adult patients with Ph+ ALL	Risk stratification for EFS by MRD good risk or poor risk groups	5 y
Conter et al (2010); AIEOP-BFM ALL 2000[68,]	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 12. Summary of Key Nonrandomized Trial Results

Study	EFS in Ph+ ALL			EFS in Ph- ALL			OS		EFS	
Arunachalam et al (2020)[67,]										
MRD Risk Stratification							Poor risk	Good risk	Poor risk	Good risk
Hazard ratio (95% CI)							Ref	2.9 (1.10-7.84)	Ref	5.4 (2.23-13.23)
Conter et al (2010); AIEOP-BFM ALL 2000; Total N[68,]	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	<.001			<.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 13. Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Conter et al (2010)[68]	4.Study population restricted to pediatric patients				
Arunachalam et al (2020)[67]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations gaps 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 14. Study Design and Conduct Limitations

Study; Trial	Selection[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Arunachalam et al (2020)[67,]	1. Participants not randomly allocated (retrospective design)	1. Not blinded to treatment assignment			1. Power calculations not reported.	
Conter et al (2010)[68,]	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.

Minimal residual disease (MRD) is also a strong prognostic factor for children and adolescents with first-relapse ALL who achieve a second remission. Patients with MRD of 0.01% or more are eligible for allogeneic hematopoietic stem cell transplantation, whereas achievement of MRD negativity may be an indication for chemotherapy.[66]

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 chromosome-positive ALL includes a prospective cohort study and case series. These studies have shown a 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 individuals with Ph-positive ALL and signs of treatment failure or disease progression is to assess for TKI resistance.

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

Populations
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 work-up 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 ABLKD 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.

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 insensitivity to second- or third-generation TKI in case series (2016).[69] 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. 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.[65]

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 chromosome-positive ALL includes case series. These studies have shown that specific imatinib-resistant variants are insensitive to one or both of the second-generation tyrosine kinase inhibitors. 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 reverse transcription-polymerase chain reaction is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive *BCR-ABL1* fusion gene quantitative testing at appropriate intervals during therapy for monitoring treatment response and remission, the evidence includes a systematic review and nonrandomized trials. The relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. Studies have shown a high sensitivity of this type of testing and a strong correlation with outcomes, including the risk of disease progression and survival, which may stratify patients to different 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 CML, with an inadequate initial response, loss of response, and/or disease progression who receive an evaluation for *ABL* SNVs to assess for TKI resistance, the evidence includes a systematic review and retrospective cohort case study. The relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. The systematic review and case series evaluated pharmacogenetics testing for TKIs and reported the presence of 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 chromosome–positive ALL who receive *BCR-ABL1* fusion gene quantitative testing at baseline before and during treatment to monitor treatment response and remission, the evidence includes a prospective cohort study and case series. The relevant outcomes are test accuracy and validity and medication use. As with CML, studies have shown a high sensitivity for this type of testing and a strong correlation with outcomes, including the risk of disease progression, which may stratify patients to different treatment options. Also, evidence of treatment resistance or disease recurrence directs a change in medication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have Ph chromosome–positive ALL and signs of treatment failure or disease progression who receive an evaluation for *ABL1* SNVs to assess for TKI resistance, the evidence includes case series. The relevant outcomes are test accuracy and 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 (NCCN) practice guidelines (v.1.2024) on chronic myelogenous leukemia outline recommend 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 15).[20] Guidelines for discontinuation of tyrosine kinase inhibitor therapy are detailed; molecular monitoring is recommended every month for the first 6 months, bimonthly during months 7-12, and quarterly

thereafter (indefinitely) for patients who remain demonstrate *BCR-ABL1* ≤0.01% International Scale (IS).

Table 15. Treatment Options for CML Based on *BCR-ABL1* Variant Profile[i,ii]

Contraindicated Single Nucleotide Variants	Treatment Recommendation
None	Ponatinib, omacetaxine, allogeneic HCT
T3151, Y253H, E255K/V, F359V/C/I,	Nilotinib
T3151/A, F317L/V/I/C, V299L	Dasatinib
T3151, V299L, G250E, F317L	Bosutinib
A337T, P465S, or F359V/I/C	Asciminib

CML: chronic myelogenous leukemia; HCT: hematopoietic cell transplantation.
[i] Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.1.2024. © 2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

The National Comprehensive Cancer Network practice guidelines (v.2.2024) on acute lymphoblastic leukemia (ALL) state that, if minimal residual disease (MRD) is being evaluated, the initial measurement should be performed on completion of induction therapy; additional time points for MRD evaluation may be useful, depending on the specific treatment protocol or regimen used. MRD is an essential component of patient evaluation during sequential therapy.[15] Treatment options based on *BCR-ABL* Mutation Profile are shown in Table 16.

Table 16. Treatment Options for ALL Based on *BCR-ABL1* Variant Profile[i,ii]

Contraindicated Single Nucleotide Variants	Treatment Recommendation
None	Ponatinib
T3151, Y253H, E255K/V, F359V/C/I, G250e	Nilotinib
T3151/A F317/L/V/I/C, V299L	Dasatinib
T3151, v299L, G250E, F317L	Bosutinib

ALL: acute lymphoblastic leukemia.
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Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03874858[a]	A Phase II, Single-arm, Multicenter Study of Full Treatment-free Remission in Patients With Chronic Myeloid Leukemia in Chronic Phase Treated With Nilotinib in First-line Therapy Who Have Achieved a Sustained, Deep Molecular Response for at Least 1 Year	124	Dec 2026
NCT03817398	Stopping Tyrosine Kinase Inhibitors (TKI) to Assess Treatment-Free Remission (TFR) in Pediatric Chronic Myeloid Leukemia - Chronic Phase (CML-CP)	110	Jun 2026 (recruiting)
NCT01784068[a]	A Single-arm, Multicenter, Nilotinib Treatment-free Remission Study in Patients With BCRABL1 Positive Chronic Myelogenous Leukemia in Chronic Phase Who Have Achieved Durable Minimal Residual Disease (MRD) Status on First Line Nilotinib Treatment (ENESTFreedom)	2015	Feb 2025 (ongoing)
NCT01698905[a]	A Phase II, Single-Arm, Open Label Study of Treatment-free Remission in Chronic Myeloid Leukemia (CML) Chronic Phase (CP) Patients After Achieving Sustained MR4.5 on Nilotinib	163	Feb 2025 (ongoing)
NCT02881086	Treatment Optimization in Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma by Individualized, Targeted and Intensified Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients	1000	Jul 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)	245	Jul 2027 (Recruiting)
Unpublished			
NCT03885830	Preliminary Evaluation of TKI Exposure-response Relationships in Real World Patients (RWPs) With Chronic Myelogenous Leukemia (CML)	150	Dec 2020 (completed)
NCT01762969	Modification of Imatinib to Other Tyrosine Kinase Inhibitors Dependent on 3-months Molecular Response of CML Patients	300	Jan 2020
NCT02001818[a]	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
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 BCRABL Currently Being Treated With First or Subsequent TKI Therapy in the UK, Ireland, or France Using NGS	400	Dec 2020
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	Jan 2022
NCT02602314	Sustained Treatment-free Remission in BCR-ABL+	450	Feb 2024

	Chronic Myeloid Leukemia: a Prospective Study Comparing Nilotinib Versus Imatinib With Switch to Nilotinib in Absence of Optimal		

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

Government Regulations

National:

There is no national coverage determination on this particular topic of testing.

Local:

L36815, MolDX: Genetic Testing for *BCR-ABL* Negative Myeloproliferative Disease. Effective on or after 07/06/2023.

This policy provides coverage for multi-gene non-NGS (Next Generation Sequencing) panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPD), and limited coverage for single-gene testing of patients with *BCR-ABL* negative myeloproliferative disease (MPD). MPD includes polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF).

For laboratories performing single gene technologies, a sequential genetic testing approach is expected. Once a positive result is obtained and the appropriate diagnosis is established, further testing should stop. Reflex testing to the next gene will be considered reasonable and necessary if the following sequence of genetic tests produce a negative result:

1. BCR-ABL negative test results, progress to #2
2. JAK 2, cv negative test results, progress to #3 or #4
3. JAK, exon 12 (JAK2 exon 12 is only done when PV is suspected)
4. CALR/MPL (CALR/MPL is only done when either ET or PMF is suspected; testing for CALR/MPL does NOT require a negative JAK2 exon 12, just a negative JAK2 V617F result)

Genetic testing of the JAK2 V617F mutation (81270) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization's diagnostic criteria for myeloproliferative disease (i.e., polycythemia vera, essential thrombocytopenia, primary myelofibrosis) **if** JAK2 V617F were identified.

Genetic testing of JAK2 exon 12 (81403), performed to identify PV, is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization's diagnostic criteria for PV, if JAK2 exon 12 testing were positive; **and**
- JAK2 V617F mutation analysis was previously completed and was negative.

Genetic testing of the CALR gene (81219) (only found in ET and PMF) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet World Health Organization's diagnostic criteria for MPD (i.e., ET, PMF) if a clonal marker were identified.

Genetic testing of the MPL gene (81402) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet World Health Organization's diagnostic criteria for MPD (i.e., ET, PMF) if a clonal marker were identified.

Note: In a single-gene sequential approach (not mandated by this policy), CALR would be a higher priority single gene test than MPL because:

- CALR mutations is more prevalent than MPL mutations in ET/PMF patients; and
- CALR mutations are reported to predict a more indolent disease course than that of patients with JAK2 mutations.

For laboratories performing next generation sequencing (NGS or "hotspot") testing platforms: Molecular testing for BCR-ABL, JAK 2, JAK, exon 12, and CALR/MPL genes by NGS is covered as medically necessary for the identification of myeloproliferative disorders.

Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include polycythemia vera (PV), essential thrombocytosis (ET), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML). The World Health Organization (WHO) further classifies PV, ET, and PMF as Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The diagnosis of an MPN is suspected based upon clinical, laboratory, and pathological findings (i.e., bone marrow morphology). MPNs are related, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells, while MPN are characterized by an increase in the number of blood cells.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/16	6/21/16	7/13/16	Joint policy established
9/1/17	6/20/17	6/20/17	Routine maintenance; no change in policy status
9/1/18	6/19/18	6/19/18	Routine policy maintenance, added reference # 41. No change in policy status.
3/1/19	12/11/18		Code 0016U added, effective 8/1/17.
3/1/20	12/17/19		Updated rationale, added references 23-33 and 60-66. Restated MPS wording, no change in coverage status.
3/1/21	12/15/20		Updated rationale, added references # 25 & 26. No change in policy status.
3/1/22	12/14/21		Rationale updated, routine maintenance, no change in policy status.
3/1/23	12/20/22		Add codes 81450, 81455 and 0400U. Added language on NGS testing, FDA approved companion diagnostic tests and PLA testing under the code section
3/1/24	12/19/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
3/1/25	12/17/24		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING-BCR-ABL1 TESTING IN CHRONIC MYELOGENOUS LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.