Genetic Testing for BCR-ABL Fusion Gene

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DESCRIPTION

The BCR-ABL fusion gene forms when pieces of chromosomes 9 and 22 break off and trade places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22, to form the BCR-ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Philadelphia Chromosome. The BCR-ABL fusion gene is found in most patients with chronic myeloid leukemia (CML) and in some patients with acute lymphoblastic leukemia (ALL).

Chronic myeloid leukemia (CML) accounts for 15% of adult leukemias. The median age of disease onset is 67 years; however, CML occurs in all age groups. In 2022, an estimated 8,860 people will be diagnosed with CML in the United States and 1,220 people will die from the disease (NCCN Chronic Myeloid Leukemia 1.2023).

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CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)] that gives rise to a BCR-ABL1 fusion gene.

There are three phases of CML which are chronic, accelerated and blastic.

- Chronic phase: there are few symptoms, and most people are diagnosed after a routine blood test reveals the characteristic blood count and differential. If not treated the disease will progress to accelerated and blastic phases.
- Accelerated and blastic symptoms include fever, bone pain, splenomegaly, fatigue, and weakness.

Acute lymphoblastic leukemia (ALL) is a heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year, with approximately 6,660 new cases and 1,560 deaths estimated in 2022. The median age of diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older. ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults (NCCN Acute Lymphoblastic Leukemia Version 1.2022).

During the 2016 WHO classification update, two new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (BCR-ABL1-like ALL or Ph-like ALL) and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iANP21).

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.

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 versus STI571 trial, major molecular response is defined as a 3-log reduction relative to the standardized

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baseline, or 0.1% BCR-ABL1 on the IS. In the assay, BCR-ABL1 transcripts are quantified relative to 1 of 3 recommended reference genes (e.g., ABL) to control for the quality and quantity of RNA and to normalize for potential differences between tests

Treatment and Response and Minimal Residual Disease
Before initiation of therapy for CML or ALL, quantification of the *BCR-ABL* transcript is necessary to establish baseline levels for subsequent quantitative monitoring of response during treatment.

Quantitative determination of *BCR-ABL1* transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment. Evaluation of trial samples has consistently shown the degree of molecular response correlates with the risk of progression. Also, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising BCR-ABL1 transcript levels predict treatment failure and the need to consider a change in management. Quantitative polymerase chain reaction-based methods and international standards for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec; Novartis), a tyrosine kinase inhibitor (TKI), was originally developed specifically to target and inactivate the Abl tyrosine kinase portion of the Bcr-Abl1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in "durable responses in [a] large proportion of the patients with a decreasing rate of relapse." As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

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

Treatment response is evaluated initially by the hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percentage of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib.[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

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methods of monitoring treatment response (sensitivity, 0.001%). Most ALL patients can be tested with Ig and T-cell receptor gene arrangement analysis, whereas only Ph-positive patients can be tested with polymerase chain reaction analysis of BCR-ABL transcripts.

Treatment Resistance

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

Structural studies of the Abl-imatinib complex have resulted in the design of second-generation Abl inhibitors, including dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis), which were initially approved by the U.S. Food and Drug Administration (FDA) for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of both agents in newly diagnosed chronic-phase patients have shown that both are superior to imatinib for all outcomes measured after 1 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 FDA has approved third-generation TKIs, ponatinib, and bosutinib. Ponatinib is indicated for the treatment of patients with T315I-positive CML or Ph-positive ALL, or for whom no other TKI is indicated. Bosutinib is indicated for Ph-positive CML with resistance or intolerance to prior therapy.

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

Molecular Resistance

Molecular resistance is most often explained as genomic instability associated with the creation of the abnormal BCR-ABL1 gene, usually resulting in point mutations within the ABL1 gene KD that affects protein kinase-TKI binding. BCR-ABL1 single nucleotide variants (SNVs) account for 30% to 50% of secondary resistance. (Note that new BCR-ABL SNVs also occur in 80% to 90% of cases of ALL in relapse after TKI treatment and in CML blast transformation.). The degree of resistance depends on the position of the variant within the KD (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

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E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance.

The presence of ABL SNVs is associated with treatment failure. A large number of variants have been detected, but extensive analysis of trial data with low-sensitivity variant detection methods has identified a small number of variants consistently associated with treatment failure with specific TKIs; guidelines recommend testing for information on these specific variants to aid in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced. Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.
Unlike imatinib, fewer variants are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al (2007) and Cortes et al (2007) studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell BCR-ABL1 variants. However, neither dasatinib nor nilotinib is effective against resistant clones with the T315I variant. Other treatment strategies are in development for patients with drug resistance.

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

Diagnosis and Pretreatment Workup of Chronic Myeloid Leukemia (CML)

Clinical Context and Test Purpose
The purpose of BCR-ABL1 testing in individuals with suspected chronic myeloid leukemia (CML)is the following:
- To inform diagnosis; and
- Establish a baseline for monitoring treatment

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

Interventions
The testing being considered is BCR-ABL1 fusion gene qualitative testing.

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

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

Review of Evidence

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. If bone marrow is not available, fluorescence in situ hybridization analysis with dual probes for BCR and ABL genes or qRT-PCR can provide qualitative confirmation of the fusion gene and its type.

Section Summary
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 Chronic Myelogenous Leukemia (CML)

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.

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 Compared with conventional cytogenetics, qRT-PCR is more than 3 logs more sensitive 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., 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.

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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.

Review of Evidence

Systematic Reviews
In 2017, Campiotti et. al., performed a systematic review of the literature to determine the incidence of chronic myeloid leukemia (CML) relapse, to identify possible factors relapse rates and to evaluate the long-term safety in CML patients with stable undetectable BCR-ABL transcript level who discontinued tyrosine kinase inhibitors (TKIs). Fifteen cohort studies, for a total of 509 patients, were included. Nine studies were at low-risk of bias. All 15 studies included only patients on imatinib. Overall weighted mean molecular relapse rate of CML was 51% (95% CI 44-58%; $I^2 = 55$). Weighted mean molecular relapse rate at 6-month follow-up was 41% (95% CI 32-51%; $I^2 = 78$). Eighty percent of molecular relapses occurred in the first 6 months. All 509 patients were alive at 2-year follow-up and only one patient (0.8%, 95% CI 0.2-1.8%; $I^2 = 0$) has progressed to a blastic crisis. The authors concluded that that imatinib discontinuation is feasible for the majority of CML patients with stable undetectable BCR-ABL transcript level. Approximately 50% of patients remain therapy-free after imatinib discontinuation. Restarting TKIs therapy was followed by a very high rate of molecular response, with no deaths 2 years after discontinuation.

Nonrandomized Studies
Several studies have used these tests to guide discontinuation of select tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML) patients who have achieved an appropriate molecular response and to monitor treatment-free remission. 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. 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% 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. The predictive relationship between early molecular response at 3 months and eventual achievement of deep molecular response with imatinib or nilotinib treatment

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was explored by Wang et al (2019) in 206 patients with chronic-phase CML., 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.[29,] Discontinuation of therapy with first- or subsequent-line dasatinib was investigated by Shah et al (2020) in the DASFREE trial., Patients were treated for a minimum of 2 years and were required to achieve dasatinib-induced MR4.5 for at least 1 year prior to study entry. At 1 year, treatment-free remission (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 degree of molecular response has also been reported to correlate with the risk of progression in patients treated with imatinib. 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.

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. A conversion factor was calculated for ddPCR to apply positive BCR-ABL1 ratios on the international scale (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 treatment-free remission at 12 months (TFR) 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.,

Atallah et al (2021) evaluated molecular recurrence after TKI discontinuation in 171 patients with CML. 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).

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 (OS).,

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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., Without a complete cytogenetic response, 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,[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. 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. 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.

Section Summary

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 Tyrosine Kinase Inhibitor Resistance in Chronic Myelogenous Leukemia

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.

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. 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.

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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.

Review of Evidence
In 2019 Xue et. al. reported on the role of additional chromosomal abnormalities (ACAs) and kinase domain (KD) mutations in the progression and outcomes of Chronic myeloid leukemia (CML) patients and the connection between them, they analyzed the ACAs and KD mutations of 219 CML patients admitted to the hospital. Cytogenetic analysis of metaphases was performed to detect ACAs, and the BCR-ABL1 KD was sequenced to detect KD mutations. Twenty-four patients (11.0%) had ACAs in addition to the BCR-ABL1 or t(9;22)(q34;q11) translocation. The most common abnormality was trisomy 8. Twelve different KD mutations were observed in 13 out of 53 imatinib-resistant patients (24.5%). p.(Y235H) (n = 3; 23.07%), p.(F359V) and p.(T315I) (n = 2; 15.38%) presented most frequently. KD mutations subtypes (p.(E255K), p.(T315I), p.(F359V), p.(M244V) and p.(L298V)) coexisted with ACAs. The incidence of CML progression was 12/22 (54.5%) in the group of patients with ACAs and/or KD mutations and 2/143 (1.4%) in the group of patients without ACAs or KD mutations (CI 95%, $P < 0.001$) and was higher in the KD mutations group than in the ACAs group ($P = 0.046$). The group of patients with ACAs and/or KD mutations had more men than the group of patients without ACAs or KD mutations ($P = 0.013$). The authors concluded that ACAs and/or KD mutations are related to CML progression and are adverse outcome factors. Their presence exhibits gender differences and is more common in males. p.(E255K), p.(T315I), p.(F359V), p.(M244V) and p.(L298V) emerge more frequently when ACAs and KD mutations coexist.

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

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study is recommended before these assays are used for monitoring in advance of treatment failure. 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. 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.

Section Summary
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 Acute Lymphoblastic Leukemia (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 (Ph+) acute lymphoblastic leukemia (ALL) is to monitor treatment response and remission.

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

Interventions
The testing 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.

Review of Evidence

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

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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.

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.[52,] The principal aim of therapy after remission is to eradicate the minimal residual disease (MRD), which is the prime cause of relapse.

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 post-remission therapy.

Arunachalam et al (2020) performed a retrospective cohort analysis of 94 patients with Ph-positive ALL. 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).

Section Summary
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, retrospective 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 Kinase DomainSingle Nucleotide Variants Associated with Tyrosine Kinase Inhibitor Resistance in Ph-Positive Acute Lymphoblastic Leukemia (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.

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

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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.

Review of Evidence

Resistance to TKIs in acute lymphoblastic leukemia (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). 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

Section Summary

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 chronic myelogenous leukemia (CML) who receive BCR-ABL1 fusion gene qualitative testing to confirm the diagnosis and establish a baseline for monitoring treatment, the evidence includes validation studies. Relevant outcome is test validity. The sensitivity of testing with reverse transcription-polymerase chain reaction is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive BCR-ABL1 fusion gene quantitative testing at appropriate intervals for monitoring treatment response and remission, the evidence includes a systematic review and nonrandomized trials. Relevant outcomes are disease-specific survival, test validity, and change in disease status. Studies have shown high sensitivity of this type of testing and a strong correlation with outcomes, including the risk of disease progression and survival, which may stratify patients to different options for disease management. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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For individuals who have a diagnosis of CML with an inadequate initial response, loss of response, and/or disease progression who receive an evaluation for ABL KD single nucleotide variants to assess for TKI resistance, the evidence includes a systematic review and retrospective cohort study. Relevant outcomes are disease-specific survival, test validity, and medication use. The systematic review and case series evaluated pharmacogenetics testing for TKIs and reported the presence of KD single nucleotide variants detected at imatinib failure. These studies have shown a correlation between certain types of variants, treatment response, and the selection of subsequent treatment options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a diagnosis of Philadelphia chromosome-positive acute lymphoblastic leukemia who receive BCR-ABL1 fusion gene quantitative testing at baseline before and during treatment to monitor treatment response and remission, the evidence includes prospective and retrospective cohort studies and case series. Relevant outcomes are disease-specific survival, test validity, and change in disease status. As with CML, studies have shown high sensitivity for this type of testing and a strong correlation with outcomes, including the risk of disease progression, which may stratify patients to different treatment options. Also, evidence of treatment resistance or disease recurrence directs a change in medication. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Philadelphia chromosome-positive acute lymphoblastic leukemia and signs of treatment failure or disease progression who receive an evaluation for ABL1 KD single nucleotide variants to assess for TKI resistance, the evidence includes case series. 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 an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Chronic Myeloid Leukemia Version 1.2023

Overview
CML is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Ph results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22] that gives rise to a BCR-ABL1 fusion gene.

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Monitoring Response to TKI Therapy and Mutations Analysis

Test	Recommendation
Bone marrow cytogenetics	• At diagnosis • Failure to reach response milestones • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate defined as an increase in BCR::ABL1 transcript >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After BCR::ABL1 (IS) ≤ 1%[2] has been achieved, every 3 months for 2 years and every 3-6 months thereafter • If there is 1-log increase in BCR::ABL1 transcript levels with MMR, qPCR should be repeated in 1-3 months

BCR-ABL1 kinase domain mutation analysis	• Chronic phase
	  ○ Failure to reach response milestones
	  ○ Any sign of loss of hematologic response
	  ○ Any sign of loss of CCyR or its molecular response correlate defined as an increase in BCR:: ABL1 transcript >1%
	  ○ 1-log increase in BCR-ABL1 transcript levels and loss of MMR
	• Disease progression to accelerated or blast phase

Discontinuation of TKI Therapy

- **Criteria for TKI Discontinuation**
  - Age ≥18 years
  - Chronic phase (CP)- CML. No prior history of accelerated phase (AP) or blast phase (CP) - CML
  - On approved TKI therapy for at least 3 years
  - Prior evidence of quantifiable BCR::ABL1 transcript
  - Stable molecular response (MR4; BCR::ABL1 ≤0.01% IS) for ≥2 years, as documented on last least 4 tests, performed at least 3 months apart
  - Access to a reliable qPCR test with a sensitivity of detection of a least MR4.5 (BCR-ABL1 ≤0.0032% IS) and that provides results within 2 weeks
  - Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7-12, and quarterly thereafter (indefinitely) for patients who remain in MRR (MR3; BCR::ABL1 ≤0.1% IS)

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– Prompt resumption of TKI within 4 weeks of loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MRR. For those who fail to achieve MMR after 3 months if TKI resumption, BCR::ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

Recommendations for Monitoring Response to TKI Therapy
qPCR (IS) is the preferred method to monitor response to TKI therapy. qPCR assays with a sensitivity of ≥4.5-log reduction from the standardized baseline is recommended for the measurement of BCR-ABL1 transcripts (CML-C). In patients with prolonged myelosuppression who may not be in complete hematologic response (CHR) due to persistent cytopenias or unexplained drop in blood counts during therapy, bone marrow cytogenetics is indicated to confirm response to TKI therapy and exclude other pathology, such as MDS or the presence of chromosomal abnormalities other than Ph.

Monitoring with qPCR (IS) every 3 months is recommended for all patients after initiating TKI therapy, including those who meet response milestones at 3, 6 and 12 months (≤10% BCR-ABL1 at 3 and 6 months, ≤ 1% BCR-ABL1 IS at 12 months, and ≤0.1% BCR-ABL1 IS at > 12 months). After CCyR (≤1% BCR-ABL1 IS) has been achieved, molecular monitoring is recommended every 3 months for 2 years and every 3 to 6 months thereafter.

Frequent molecular monitoring with qPCR (IS) can help to identify non-adherence to TKI therapy early in the treatment course. Since adherence to TKI therapy is associated with better outcomes frequent molecular monitoring is essential if there are concerns about the patient's adherence to TKI therapy. In patients with deeper molecular responses (MMR and better) and who are compliant with TKI therapy, the frequency of molecular monitoring can be reduced, though the optimal frequency is unknown. Molecular monitoring of response to TKI therapy more frequently than every 3 months is not presently recommended.

BCR-ABL1 Kinase Domain Mutation Analysis
Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of secondary resistant to TKI therapy and are associated with poor prognosis and higher risk of disease progression. E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse. Among the BCR-ABL1 kinase domain mutations, T315I confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib. The T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib. G250E, and V299L mutants are resistant to bosutinib.

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BCR-ABL1 kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate response to first-line or second line TKI therapy. The guidelines recommend BCR- kinase domain mutational analysis for patients who do not depending on whether they occur in Ph-positive or Ph-negative clones. Therefore, these results are not indicative of the frequency of mutations in cancer-associated genes in patients with CP-CML at diagnosis and results are not definitive.

Specific Considerations for Children with CML

CML accounts for less than 3% of all pediatric leukemias. In general, children are diagnosed at a median age of 11 to 12 years, with approximately 10% presenting in advanced phase. Due to its rarity, there are no evidence-based recommendations for the management of CML in the pediatric population. Many pediatric oncologists follow treatment guidelines that are designed for the adult patients. However, clinical presentations and host factors are different between children and adults, and several factors should be considered when treatment pediatric patients with CML.

Imatinib, dasatinib and nilotinib are currently approved for treatment of CML in children. Higher dose imatinib (340 mg/m^2) has also been shown to be effective and well tolerated in children. There are very little data on the safety and efficacy of bosutinib and ponatinib in children.

The validity of prognostic scores (e.g., Sokal, Euro) for risk assessment or to make treatment decisions has not been established in the pediatric population. The ELTS score has demonstrated better differentiation of PFS than Sokal and Euro scores in children treated with imatinib.

Acute Lymphoblastic Leukemia Version 1.2022

Diagnosis

Clinical Presentation and Diagnosis

Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning. Subtypes of B-ALL with recurrent genetic abnormalities include the following: hyperdiploidy (51–65 chromosomes); hypodiploidy (<44 chromosomes); t(9;22)(q34;q11.2), BCR-ABL1; t(4;11) and other KMT2A rearranged, t(v;11q23); t(12;21)(p13;q22), ETV6-RUNX1; t(1;19)(q23;p13.3), TCF3-PBX1; and t(5;14)(q31;q32), IL3-IGH.33 During the 2016 WHO classification update, two new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (BCR-ABL1–like ALL or Ph-like ALL)34-36 and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21).34,37 Two new provisional entities were also added to T-cell ALL (T-ALL): early T-cell precursor (ETP) lymphoblastic leukemia and natural killer (NK) cell lymphoblastic leukemia/lymphoma.34 The Ph-like ALL, B-ALL with iAMP21 and ETP T-ALL subtypes are no longer considered provisional entities.

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Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), and interphase fluorescence in situ hybridization (FISH) assays that include probes capable of detecting the genetic abnormalities and/or reverse transcriptase-polymerase chain reaction (RT-PCR) testing, using qualitative or quantitative methods to measure transcript sizes (i.e., p190 vs p210) of BCR-ABL1 in B-ALL. If samples are BCR-ABL1/Ph- negative or Ph-like, comprehensive testing by next-generation sequencing (NGS) for other gene fusions and pathogenic mutations associated with Ph-like ALL is recommended. In cases of aneuploidy or failed karyotype, additional assessment may include chromosomal microarray (CMA)/array comparative genomic hybridization (aCGH). The translocation t(12;21)(p13;q22) is typically cryptic by karyotyping and requires FISH or PCR to be identified.

Cytogenetics	Gene	Frequency in Adults	Frequency in Children
T(9,22)(q34;q11) Philadelphia chromosome (Ph)	BCR-ABL1	25%	2%-4%
BCR-ABL1-like/Ph-like	Various	10-30%	15%

BCR-ABL1-like or Ph-like ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis.

Cytogenetic Risk Groups for B-ALL

Poor Risk

- BCR-ABL1 – like (Ph-like) ALL
  - JAK-STAT (CRLF2r, EPORr, JAK1/2/3r, TYK2r, mutations of SH2B3, IL7R, JAK1/2/3
  - ABL class (rearrangements of ABL1, ABL2, PDGFRA, PDGFRB, FGFR)
  - Other (NTRKr, FLT3r, LYNr, PTL2Br)

Treatment Options Based on BCR-ABL1 Mutation Profile

Therapy	Contraindicated Mutations
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I or G250E
Ponatinib	None

Minimal/Measurable Residual Disease Assessment

The most frequently employed methods of MRD assessment include at least 6-color flow cytometry assays specially designed to detect abnormal MRD immunophenotypes, real-

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time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (e.g., BCR-ABL1), and NGS-based assays to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.

NCCN Recommendations for Risk Assessment in ALL

Although some debate remains regarding the risk stratification approach to ALL, the panel suggests the following approaches for defining risk in these patients. The NCI defines the age range for AYA patients as 15 to 39 years. For Ph-positive ALL, the AYA patient population is grouped with fit, adult patients aged less than 65 years. However, additional considerations for the management of ALL in AYA can be found in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology. For Ph-negative ALL, the AYA patient population is considered separately from the adult population (defined as age ≥40 years). Given the poor prognosis associated with Ph-positive ALL and the wide availability of agents that specifically target the BCR-ABL kinase, initial risk stratification for all patients (AYA or adult) is based on the presence or absence of the t(9;22) chromosomal translocation and/or BCR-ABL fusion protein. For adult patients with ALL (Ph-positive or Ph-negative), these guidelines further stratify patients by age, using 65 years as the cutoff, to guide treatment decisions. However, chronologic age alone is a poor surrogate for determining patient fitness for therapy. Patients should, therefore, be evaluated on an individual basis. In the NCCN Guidelines for ALL, specific age references are not included for AYA and adult categories, considering that age is not a firm reference point and some of the recommended regimens have not been comprehensively tested across all ages. AYA patients and adult patients younger than 65 years of age (or for those with no substantial comorbidities) with Ph-negative ALL can be further categorized as having high-risk disease, which may be particularly helpful when consolidation with allogeneic HCT is being considered. Patients may be considered high risk if they have positive MRD, an elevated WBC count (≥30 × 109/L for B-cell lineage; ≥100 × 109/L for T-cell lineage), or presence of poor-risk cytogenetics as previously defined. The absence of all poor-risk factors is considered standard risk. Evaluation of WBC count and age for determination of prognosis should ideally be made in the context of treatment protocol-based risk stratification. These additional risk stratification parameters are generally not used for patients aged 65 years or older (or for patients with substantial comorbid conditions) with Ph-negative ALL. Similar to AYA patients, elevated WBC count (≥30 × 109/L for B-cell lineage; ≥100 × 109/L for T-cell lineage) has been considered a high-risk factor based on some earlier studies. However, studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors and MRD assessments are considered. Data showing the effect of WBC counts on prognosis in adult patients with ALL are less firmly established than in the pediatric population and likely superseded by MRD quantification after treatment. Therefore, adult patients with ALL may not necessarily be classified as high risk based on high WBC count alone.

Surveillance

After completion of the ALL-treatment regimen (including maintenance therapy), the panel recommends surveillance at regular intervals to assess disease status. During the

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first year after completion of therapy, patients should undergo a complete physical examination (including a testicular examination) and blood tests (CBC with differential). Liver function tests should be performed until normal values are achieved. An assessment of bone marrow aspirate can be considered as clinically indicated at a frequency of 3 to 6 months for the first 5 years; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be considered. For Ph-positive ALL, periodic quantification of the BCR-ABL1 transcript should be determined, During the second year after completion of therapy a physical examination (including a testicular examination) and blood tests (CBC with differential) should be performed every 3 to 6 months. During the third year (and beyond) after completion of therapy, physical examination (including a testicular examination) and blood tests (CBC with differential) can be performed every 6-12 months or as clinically indicated.

Role of MRD Evaluation

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Patients who experienced a CR according to morphologic assessment alone can potentially harbor a large number of leukemia cells in the bone marrow: up to 10^{10} malignant cells.

The most frequently used methods for MRD quantification include multiparameter flow cytometry (e.g., 6 color or higher) to detect leukemia-associated immunophenotypes, PCR assays to detect fusion genes (e.g., BCR-ABL1) and NGS-based assays to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes. Assays to detect alternative leukemia-specific fusion genes specifically using NGS (as opposed to PCR) are also in development but are not recommended for MRD quantification outside the context of a clinical trial. The NCCN Panel acknowledges FDA approval of an NGS-based MRD test based on quantification of immunoreceptor genes in patients with ALL, but panel members agreed that both multiparameter flow cytometry or this FDA-approved NGS approach are suitable methods for MRD quantification.

Current multi-parameter flow cytometry methods can detect leukemic cells at a sensitivity threshold of fewer than 10-4 (<0.01%) bone marrow mononuclear cells (MNCs), and PCR/NGS methods can detect leukemic cells at a sensitivity threshold of fewer than 10-6 (<0.0001%) bone marrow MNCs. The concordance rate for quantifying MRD between these methods is generally high at disease burdens 10-4 (>0.01%), but NGS is able to detect MRD at lower thresholds. In a study that analyzed MRD using both flow cytometry and PCR techniques in 1375 samples from 227 patients with ALL, the concordance rate for MRD assessment (based on a detection threshold of <1 × 10-4 for both methods) was 97%.382 In another study, both flow cytometry and high-throughput sequencing techniques were used to analyze MRD at a threshold of 0.01% in samples from 619 patients with pediatric B-ALL. At the 0.01% threshold, the concordance between both methods was high, but high-throughput sequencing was able to detect MRD at lower thresholds. The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.

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However, this practice could lead to an increase in cost without a clear directive in terms of modification of treatment. Numerous studies in both childhood and adult ALL have shown the prognostic importance of postinduction (and/or post-consolidation) MRD measurements in predicting the likelihood of disease relapse. New multiplexed PCR and NGS for MRD are emerging methodologies.

NCCN Recommendations for MRD Assessment
Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. The preferred sample for MRD assessment is the first small volume (up to 3 mL) pull or early pull of the bone marrow aspirate, if feasible. If the patient is not treated at an academic medical center, there are commercially available tests that should be used for MRD assessment. Six-color flow cytometry can detect leukemic cells at a sensitivity threshold of fewer than 1 × 10-4 (<0.01%) bone marrow MNCs, and PCR or NGS methods can detect leukemic cells at a sensitivity threshold of MNCs. T fewer than 1 × 106 (< 0.0 00 1%) bone marrow he concordance rate for detecting MRD between these methods is generally are not suitable. high . Methods not achieving these sensitivity levels For flow cytometric analysis of MRD, if immunotherapy has been used (eg, rituximab, blinatumomab, InO , tisagenle brexucabtagene autoleucel cleucel, or), the lab performing the MRD assessment should be notified

The timing of MRD assessment varies depending on the ALL-treatment protocol used and may occur during or after completion of induction therapy. Therefore, it is recommended that the initial measurement be performed on completion of induction therapy; additional time points for MRD evaluation should be guided by the treatment protocol or regimen used. Importantly, the treatment protocol or regimen both immunophe notype (Bvs. Tlineage) and genotype may impact the prognostic significance of various levels of MRD at different time points, reflecting the influence of these variables on the kinetics of response to therapy. This further highlights the importance of referring to the protocol or regimen being used when interpreting MRD results.

An increase in frequency of serial monitoring of MRD may be useful in patients with molecular relapse and low-level disease. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT is preferred.

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

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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 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.

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.

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary

Chronic Myeloid Leukemia (CML)
BCR-ABL1 testing for the presence of the fusion gene may be considered **medically necessary** for diagnosis of chronic myeloid leukemia (CML).

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BCR-ABL1 testing messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals may be considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission meeting the following criteria:

- Initiation of treatment and at regular intervals during treatment (every 3 months) with any of the following tyrosine kinase inhibitor (TKI) inhibitor therapies:
    - Imatinib (Gleevac)
    - Nilotinib (Tasigna)
    - Dasatinib (Sprycel)
    - Bosutinib (Bosulif); **or**
- After BCR-ABL1 (IS) ≤ 1% has been achieved (CCyR [complete cytogenetic response] correlates with BCR-ABL1 [IS] ≤ 1%) every 3 months for 2 years and every 3-6 months thereafter; **or**
- If there is 1-log increase in BCR-ABL1 transcript levels with major molecular response (MMR), qPCR should be repeated in 1-3 months; **or**
- The individual is in chronic phase of disease **and**
    - Are on TKI inhibitor therapy (see above); **and**
    - Have failed to reach treatment response milestones; **or**
    - Any sign of loss of response (defined as hematology or cytogenetic relapse) to TKI inhibitor therapy; **or**
    - Experience 1-log increase in BCR-ABL1 transcript levels and loss of MMR (major molecular response).

Evaluation of ABL kinase domain (KD) single nucleotide variants to assess patients for tyrosine kinase inhibitor (TKI) resistance may be considered **medically necessary** 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 (ALL)

BCR-ABL1 testing may be considered **medically necessary** for individuals with acute lymphoblastic leukemia (ALL) for any of the following indications:

- Individuals with Ph positive (Ph+) acute lymphoblastic leukemia (ALL) for disease evaluation, risk stratification and treatment planning; **or**
- Minimal/measurable residual disease assessment performed on completion of induction therapy and additional time points for MRD evaluation should be guided by the treatment protocol or regimen used; **or**
- After completion of the ALL-treatment regimen (including maintenance therapy) to assess disease status, an assessment of bone marrow aspirate can be considered as clinically indicated at a frequency of 3 to 6 months for the first 5 years; if bone marrow aspirate is performed flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests and MRD assessments should be carried out.

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Not Medically Necessary
BCR-ABL testing not meeting the above criteria and for all other indications is considered **not medically necessary**.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81170 ABL1 (ABL pronto-oncogene 1, non-receptor tyrosine kinase) (eg, 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
- 81401 Molecular pathology procedure Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis] or detection of a dynamic mutation disorder/triplet repeat) (Includes ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib resistance) T315I variant)
- 0016U Oncology (hematolymphoid neoplasia) RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
- 0040U BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

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POLICY HISTORY

Date	Reason	Action
August 2022	Annual Review	Policy Revised
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Renewed
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Revised
August 2016	New Policy	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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