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Medical Policy Manual

Topic: BCR-ABL1 Testing for Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia

Date of Origin: March 31, 2011

Section: Genetic Testing

Last Reviewed Date: April 2014

Policy No: 27

Effective Date: July 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

In the treatment of Philadelphia chromosome (Ph)-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 point mutations related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

Chronic Myelogenous (Myeloid) Leukemia (CML)

Chronic myelogenous (myeloid) leukemia is a malignancy of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias. In its natural course, the disease progresses through chronic, accelerated, and finally blast phases (blast crisis) in which the disease behaves like an acute leukemia, with rapid progression and short survival. Most often, CML is diagnosed in the chronic phase. 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.[1]

Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is the most common childhood tumor, and represents 75-80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The median age at diagnosis is 14 years; 60% of patients are diagnosed at less than 20 years of age. 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 ~80%. The long term prognosis among adults is poor, with cure rates of 30-40%, 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, as compared to adult ALL.

Disease Genetics

Philadelphia 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 gene characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as *BCR-ABL1*, are more common.[2] In ALL, the Philadelphia chromosome is found in 3% of children and 25-30% 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 chronic myeloid leukemia. 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.

Treatment and Response and Minimal Residual Disease

Newly diagnosed Ph1-positive CML is typically treated with tyrosine kinase inhibitors (TKI), i.e., drugs that bind to the tyrosine kinase enzyme and inhibit its activity in a competitive fashion.[3,4] Examples of TKIs that have received U.S. Food and Drug Administration (FDA) approval for the treatment of newly diagnosed Ph1-positive CML in the chronic phase include: imatinib (Imatinib mesylate - Gleevec®, Novartis Oncology), dasatinib (Sprycel®, Bristol-Myers Squibb), nilotinib (Tasigna®, Novartis Oncology), bosutinib (Bosulif®, Pfizer), and ponatinib (Iclusig®, Ariad). Imatinib, nilotinib, and dasatinib are approved as first line therapies.[4] Bosutinib is not approved for first-line therapy. Ponatinib has activity against T315I mutations and is generally used in patients who have failed multiple TKIs.

<u>Chronic Myelogenous (Myeloid) Leukemia (CML)</u>

Treatment response in CML is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percent of cells with Ph-positive metaphase [highly condensed] chromosomes in a bone marrow aspirate) and then by molecular response to measure small amounts of *BCR-ABL1* transcripts to confirm major molecular response (MMR, or ≤0.1% *BCR-ABL1* transcripts) and deeper molecular responses.[5] For CML patients, complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by 6-12 months after initial treatment with TKIs imatinib.

<u>Acute Lymphoblastic Leukemia (ALL)</u>

For ALL patients, it has been well established that most "good responders" that are considered to be in morphologic remission, but relapse, may still have considerable levels of leukemia cells, referred to as "minimal residual disease" or MRD. Among children with ALL who achieve a complete response by morphologic evaluation after induction therapy, approximately 25-50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (which affords a sensitivity of MRD detection of 0.01%), or PCR-based analyses (Ig and T-cell receptor gene rearrangements or analysis of BCR-ABL transcripts), which are the most sensitive method of monitoring treatment response, with a sensitivity of 0.001%.[6] Ig and T-cell receptor gene arrangement analysis is applicable for almost all ALL patients whereas PCR analysis of BCR-ABL transcripts is applicable only in Ph-positive patients. With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60-80% of patients achieving complete remission, significantly lower than that achieved in Ph-chromosome-negative ALL.[7] The inclusion of TKIs to frontline induction chemotherapy has improved CR rates, exceeding 90%.[7]

Resistance

Imatinib treatment does not usually result in complete eradication of malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. In addition, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. When the initial response to treatment is inadequate or there is a loss of response, resistance mutation 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.[5,8] The same challenges occur with second-generation TKIs, including dasatinib and nilotinib.

According to the National Comprehensive Cancer Network (NCCN), "Dasatinib, nilotinib, and bosutinib are active against many of the imatinib-resistant BCR-ABL1 kinase domain mutations, except T315I, and are effective treatment options for patients with chronic phase (CP)-CML resistant to standard-dose imatinib. In addition, dasatinib is effective for patients with CP-CML resistant to high-dose imatinib. Bosutinib has shown potent activity in patients resistant to dasatinib (F317L) and nilotinib (Y253H and F359C/I/V). Ponatinib has demonstrated activity in patients with E225K/V, F317L, F359V, G250E, M351T, T315I, and Y253H mutations."

In a recent follow-up study of nilotinib by le Coutre et al., 137 patients with accelerated phase CML were evaluated after 24 months.[9] Sixty-six percent of patients maintained major cytogenetic responses at 24 months. The estimates of overall and progression-free survival rates at 24 months were 70% and 33%, respectively. Grade 3/4 neutropenia and thrombocytopenia were each observed in 42% of patients.

Rarely, other acquired cytogenetic abnormalities such as *BCR-ABL* gene amplification and protein overexpression have also been reported.[10] Resistance unrelated to kinase activity may result from additional oncogenic activation or loss of tumor suppressor function, and may be accompanied by additional karyotypic changes.[8]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the

Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

I. Diagnosis and monitoring of chronic myeloid leukemia (CML)

A. Diagnosis of CML

BCR/ABL1 qualitative testing for the presence of the fusion gene may be considered **medically necessary** for the diagnosis of CML(detection of the Philadelphia chromosome and distinction between molecular variants).

B. Monitoring of CML

1. *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals* during therapy may be considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission.

2. Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be considered **medically necessary** when there is inadequate initial response to treatment or any sign of loss of response*; and/or when there is progression of the disease to the accelerated or blast phase.

3. Evaluation of *ABL* kinase domain point mutations is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

II. Monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)

A. *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals* during therapy may be considered **medically necessary** for monitoring of treatment response and remission in patients with Philadelphia chromosome-positive ALL.

B. Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be considered **medically necessary** in patients with Philadelphia chromosome-positive ALL when there is inadequate initial response to treatment or any sign of loss of response.

C. Evaluation of *ABL* kinase domain point mutations is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

POLICY GUIDELINES

Diagnosis

- Qualitative molecular confirmation of the cytogenetic diagnosis (i.e., detection of the Philadelphia chromosome) is necessary information for the accurate diagnosis of CML.

- Identification of the Philadelphia chromosome is not necessary for the diagnosis of ALL, however, molecular phenotyping is generally performed at the time of initial assessment (see determining baseline RNA transcript levels and subsequent monitoring).

- Distinction between molecular variants (i.e., p190 vs. p210) is necessary information for accurate results in subsequent monitoring assays.

Determining Baseline RNA Transcript Levels and Subsequent Monitoring

Determination of *BCR-ABL1* messenger RNA transcript levels should be done by quantitative real-time reverse transcription polymerase chain reaction-based assays, and reported results should be standardized according to the International Scale [IS].

- For CML, testing is appropriate at baseline before the start of imatinib treatment; every 3 months for 3 years, then every 3-6 months thereafter. Without attainment of 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 as well and will likely also be applied to bosutinib and ponatinib. See Rationale for more information.

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

TKI Resistance

For CML, inadequate initial response to tyrosine kinase inhibitors is defined as failure to achieve partial cytogenetic response (PCyR) or *BCR-ABL1* transcripts ≤ 10% [IS] at 3 and 6 months or complete cytogenetic response (CCyR) at 12 and 18 months.[4]

Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis.

Loss of response to tyrosine kinase inhibitors is defined as hematologic relapse, cytogenetic relapse or 1 log increase in *BCR-ABL1* transcript ratio, or loss of major molecular response(>0.1% *BCR-ABL1* transcripts or ≥ 3-log reduction in *BCR-ABL1* mRNA from the standardized baseline).

Kinase domain mutation testing is usually offered either as a single test to identify T315I mutation or as a panel (which includes T315I) of the most common and clinically important mutations.

SCIENTIFIC EVIDENCE

Literature Appraisal

Various types of laboratory tests involving *BCR-ABL1* detection are associated with chronic myelogenous leukemia (CML) and have different clinical uses. Briefly, these are:

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 (FISH; acceptable in the absence of sufficient sample for karyotyping).
2. Monitoring *BCR-ABL1*RNA transcripts for residual disease during treatment/disease remission; relevant, standardized test technology is quantitative RT-PCR. Note that a baseline measurement after confirmation of CML diagnosis and before treatment begins is strongly recommended.
3. Identification and monitoring of mutations for drug resistance at response failure/disease progression; various test technologies are in use (not standardized).

Diagnosis/Pretreatment Work-up

CML

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.[11] 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. Baseline measurement of *BCR-ABL* transcript levels are recommended as part of the initial evaluation, providing confirmation of the fusion gene, ensuring that it is detectable (rare variants requiring non-standard probes may occur), as well as a baseline for monitoring response to treatment.

ALL

The diagnosis of ALL is made by demonstrating 20% or greater bone marrow lymphoblasts. Demonstration of the BCR-ABL fusion gene is not essential to diagnosis; 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.[7]

Monitoring for Residual Disease during Treatment/Disease Remission

CML

Quantitative RT-PCR measurement of *BCR-ABL1* RNA transcript levels is the method of choice for measuring response to treatment because of the high sensitivity of the method and strong correlation with outcomes.[4] Quantitative RT-PCR testing can be conducted on peripheral blood, eliminating the need for bone marrow sampling. The goal of treatment is complete molecular response (CMR; no detectable *BCR-ABL* transcript levels (0.1%) by quantitative RT-PCR). However, only a small minority of patients achieve CMR on imatinib.[12] More often, patients achieve a major molecular response (MMR; a 3-log reduction from the standardized baseline of the International Scale). Results from the IRIS trial 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 compared to patients who had neither.[13] At 8 years' follow-up, none of the patients who achieved a MMR at 1 year progressed to the

accelerated phase of disease or to a blast crisis. Similar near absence of progression in patients who achieved an MMR has been reported in registration studies of nilotinib and dasatinib.[12,14,15]

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 3 years, then every 3-6 months thereafter.[4,16] 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 additional TKIs dasatinib, nilotinib, bosutinib, and ponatinib.[4]

ALL

Despite significantly higher complete remission (CR) rates with the use of TKIs in Philadelphia chromosome-positive ALL, the response is typically short-lived and relapses are common.[7] The principal aim of post-remission therapy is eradicating minimal residual disease, which is the prime cause for relapse. Studies in both children and adults with ALL have demonstrated a strong correlation between minimal residual disease (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 complete remission with contemporary post-remission therapy.[17] A study of 3,184 B-cell ALL children enrolled in the 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.[18] Patients with MRD less than 0.01% on day 33 (42%) had a 5-year event free survival of 92.3% (+/-0.9%).

NCCN recommendations state that the timing of when to test for MRD depends on the ALL chemotherapy regimen used, and may occur during or after completion of induction therapy, and at additional time points depending upon the chemotherapy regimen used.

MRD is also a strong prognostic factor for children and adolescents with first-relapse ALL who achieve a second remission.[17] Patients with MRD 0.01% or more are eligible for allogeneic hematopoietic stem cell transplantation, whereas achievement of MRD negativity may be an indication to deter transplantation.

<u>Identification of BCR-ABL1 Kinase Domain (KD) Mutations for CML</u>

Screening for *BCR-ABL1* kinase domain point mutations (i.e. single nucleotide polymorphisms) in chronic phase CML is recommended for patients with inadequate initial response to TKI treatment, those with evidence of loss of response, and for patients who have progressed to accelerated or blast phase CML.[4] The focus of the following discussion is on kinase domain point mutations and treatment outcomes.

Systematic Reviews/Meta-Analyses

- In 2010, the Agency for Healthcare Research and Quality published a systematic review on *BCR-ABL1* pharmacogenetic testing for tyrosine kinase inhibitors in CML.[3] Thirty-one publications of BCR-ABL1 testing met the eligibility criteria and were included in the review (20 of dasatinib, 7 of imatinib, 3 of nilotinib, and 1 with various TKIs). The report concluded that the presence of any *BCR-ABL1* mutation does not predict differential response to TKI therapy, although the presence of

the T315I mutation uniformly predicts TKI failure. However, during the public comment period the review was strongly criticized by respected pathology organizations for lack of attention to several issues that were subsequently insufficiently addressed in the final report. Importantly, the review grouped together studies that used kinase domain mutation screening methods with those that used targeted methods, and grouped together studies that used mutation detection technologies with very different sensitivities. The authors dismissed the issues as related to analytic validity and beyond the scope of the report. However, in this clinical scenario assays with different intent (screening vs. targeted) and assays of very different sensitivities may lead to different clinical conclusions, so an understanding of these points is critical.

- Branford et al. summarized much of the available evidence regarding kinase domain mutations detected at imatinib failure, and subsequent treatment success or failure with dasatinib or nilotinib.[19] 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 60-66% of all mutations. However, preexisting or emerging mutations T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. 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.[20] However these mutations do not correspond to clinical significance, and based on clinical studies, the majority of imatinib-resistant mutations remain sensitive to dasatinib and nilotinib.

  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 mutationsY253H, 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 mutations. 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; no data are available regarding mutations developing during first-line therapy with dasatinib or nilotinib.[21]

Nonrandomized Studies

Treatment recommendations based on the identified nonrandomized trials for *ABL* kinase domain mutational analysis following inadequate initial response are described in the table below. Mutation testing is also recommended for progression to accelerated or blast phase CML.

Treatment options based on BCR-ABL1 Kinase Domain point mutation status at imatinib treatment	
Mutation	**Treatment Recommendation**
T315I	Ponatinib*, HSCT or clinical trial
V299L, T315A, F317L/V/I/C	Consider nilotinib or bosutinib* rather than dasatinib
Y253H, E255K/V, F359V/C/I	Consider dasatinib or bosutinib* rather than nilotinib
Any other mutation	Consider high dose imatinib, or dasatinib, nilotinib, or bosutinib*

*Recently approved; added in advance of NCCN update, from which guidelines this table is modified. Bosutinib active across *BCR-ABL1* mutations including dasatinib- and nilotinib- resistant mutations

except T315I, and after treatment failure with imatinib, dasatinib, or nilotinib;[22,23] ponatinib active in treatment-resistant patients with T315I mutation.[20,24]

Identification of BCR-ABL1 Kinase Domain (KD) Mutations for ALL

Unlike in CML, resistance in ALL to TKIs is less well studied. Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or by competition of other coexisting subclones.[7] In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

- The 2014 NCCN practice guidelines regarding chronic myelogenous leukemia (CML) recommended methods for diagnosis and treatment management of CML, including *BCR-ABL1* tests for diagnosis, monitoring, and *ABL* kinase domain mutations.[4,8,16,25] Other types of mutations in addition to 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 mutations is not recommended[8,21] by the U.S. Association for Molecular Pathology .

- The 2013 NCCN practice guidelines regarding 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[26]. Additional time points for MRD evaluation may be useful depending on the specific treatment protocol or regimen used.

Summary

While the existing evidence is associational in nature, the body of evidence that has accumulated, the consequences of the management decisions involved, and recommendations from clinical practice guidelines support the medical necessity of the use of the assays as described in the Policy Criteria.

Chronic Myelogenous (Myeloid) Leukemia (CML)

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 Philadelphia chromosome (Ph) is not found, and to identify the type of fusion gene. 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. Therefore, *BCR/ABL1* qualitative testing for the presence of the fusion gene may be considered medically necessary for diagnosis of CML.

Monitoring

During treatment with tyrosine kinase inhibitors, quantitative determination of *BCR-ABL1*transcript levels 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 (IS) for reporting have been recommended and adopted for treatment monitoring. Therefore, *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals during therapy may be considered medically necessary for monitoring of CML treatment response and remission.

Treatment Failure

The presence of ABL kinase domain point mutations is associated with treatment failure; a large number of mutations have been detected, but extensive analysis of trial data with low-sensitivity mutation detection methods has identified a small number of mutations that are consistently associated with treatment failure with specific tyrosine kinase inhibitors; guidelines recommend testing for, and using information regarding these specific mutations in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography (DHPLC) screening to reduce the number of samples that need to be sequenced. Targeted methods that detect the mutations of interest for management decisions are also acceptable if designed for low sensitivity. High sensitivity assays are not recommended. Therefore, evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be considered medically necessary when there is inadequate initial response to treatment or any sign of loss of response and/or when there is progression of the disease to the accelerated or blast phase. Evaluation of *ABL* kinase domain point mutations is considered investigational for monitoring in advance of signs of treatment failure or disease progression.

Other uses and other types of assays are considered investigational as there is inadequate evidence to determine the impact of testing on health outcomes.

Acute Lymphoblastic Leukemia (ALL)

Diagnosis

The presence of the *BCR-ABL1* fusion gene is not necessary to establish a diagnosis of ALL. However, before initiation of therapy, identification of the *BCR-ABL* transcript is necessary for risk stratification and quantification to establish baseline levels for subsequent monitoring of response during treatment.

Monitoring

During treatment with tyrosine kinase inhibitors, quantitative determination of *BCR-ABL1* transcript levels 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. For ALL, the optimal timing remains unclear, and depends upon the chemotherapy regimen used. Therefore, *BCR/ABL1* testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals during therapy may be considered medically necessary for monitoring of acute lymphoblastic leukemia treatment response and remission.

Treatment Failure

Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis. Therefore, evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be considered medically necessary when there is inadequate initial response to treatment or any sign of loss of response. The evaluation of *ABL* kinase domain point mutations is considered investigational for monitoring in advance of signs of treatment failure or disease progression.

REFERENCES

1. Karbasian Esfahani, M, Morris, EL, Dutcher, JP, Wiernik, PH. Blastic phase of chronic myelogenous leukemia. *Curr Treat Options Oncol*. 2006 May;7(3):189-99. PMID: 16615875
2. Mullighan, CG. The molecular genetic makeup of acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2012;2012:389-96. PMID: 23233609
3. Agency for Healthcare Research and Quality ©2010. Technology Assessment: Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. Issue date: 2010. Available at: http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=76&bc=BAAgAAAAAAAA&. Accessed on 04/2012.
4. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Chronic Myelogenous Leukemia. V.3.2014. [cited 03/17/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
5. National Cancer Institute. Chronic Myelogenous Leukemia Treatment (PDQ®). [cited 04/2012]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional
6. Campana, D. Should minimal residual disease monitoring in acute lymphoblastic leukemia be standard of care? *Curr Hematol Malig Rep*. 2012 Jun;7(2):170-7. PMID: 22373809
7. Fielding, AK, Zakout, GA. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Curr Hematol Malig Rep*. 2013 Jun;8(2):98-108. PMID: 23475624
8. Jones, D, Kamel-Reid, S, Bahler, D, et al. Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. *J Mol Diagn*. 2009 Jan;11(1):4-11. PMID: 19095773
9. le Coutre, PD, Giles, FJ, Hochhaus, A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*. 2012 Jun;26(6):1189-94. PMID: 22076466
10. Walz, C, Sattler, M. Novel targeted therapies to overcome imatinib mesylate resistance in chronic myeloid leukemia (CML). *Crit Rev Oncol Hematol*. 2006 Feb;57(2):145-64. PMID: 16213151
11. Cortes, J, Kantarjian, H. How I treat newly diagnosed chronic phase CML. *Blood*. 2012 Aug 16;120(7):1390-7. PMID: 22613793
12. Radich, JP. Measuring response to BCR-ABL inhibitors in chronic myeloid leukemia. *Cancer*. 2012 Jan 15;118(2):300-11. PMID: 21717440
13. Druker, BJ, Guilhot, F, O'Brien, SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006 Dec 7;355(23):2408-17. PMID: 17151364
14. Saglio, G, Kim, DW, Issaragrisil, S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010 Jun 17;362(24):2251-9. PMID: 20525993

15. Kantarjian, H, Shah, NP, Hochhaus, A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010 Jun 17;362(24):2260-70. PMID: 20525995
16. Baccarani, M, Cortes, J, Pane, F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2009 Dec 10;27(35):6041-51. PMID: 19884523
17. Campana, D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2010;2010:7-12. PMID: 21239764
18. Conter, V, Bartram, CR, Valsecchi, MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. 2010;115:3206-14. PMID: 20154213
19. Branford, S, Melo, JV, Hughes, TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? *Blood*. 2009 Dec 24;114(27):5426-35. PMID: 19880502
20. Cortes JE, Kim DW, Pinilla-Ibarz J et al. A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-up of the PACE Trial. American Society of Hematology 54th Annual Meeting, December 2012 2012:Abstract 163.
21. Alikian, M, Gerrard, G, Subramanian, PG, et al. BCR-ABL1 kinase domain mutations: methodology and clinical evaluation. *Am J Hematol*. 2012 Mar;87(3):298-304. PMID: 22231203
22. Khoury, HJ, Cortes, JE, Kantarjian, HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012 Apr 12;119(15):3403-12. PMID: 22371878
23. Cortes, JE, Kantarjian, HM, Brummendorf, TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011 Oct 27;118(17):4567-76. PMID: 21865346
24. Cortes, JE, Kantarjian, H, Shah, NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012 Nov 29;367(22):2075-88. PMID: 23190221
25. Soverini, S, Hochhaus, A, Nicolini, FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood*. 2011 Aug 4;118(5):1208-15. PMID: 21562040
26. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Acute Lymphoblastic Leukemia. V.3.2013. [cited 03/17/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/all.pdf

CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia)

CODES	NUMBER	DESCRIPTION
		translocation analysis; major breakpoint, qualitative or quantitative
	81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
	81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
	81401	Molecular pathology procedure, Tier 2, Level 2
	81403	Molecular pathology procedure, Tier 2, Level 4
HCPCS	None	