Protocol

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

(20485)

(Formerly BCR-ABL1 Testing for Diagnosis, Monitoring, and Drug Resistance Mutation Detection in Chronic Myelogenous Leukemia [CML])

Medical Benefit		**Effective Date**: 07/01/14	**Next Review Date**: 05/15
Preauthorization	Yes	**Review Dates**: 05/13, 05/14	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is required.*** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

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.

Background

Disease

CML: Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within three to five years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, very high or very low platelet counts, etc. (1) From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow. (2)

ALL: Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is the most common childhood tumor, and represents 75% to 80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The median age at diagnosis is 14 years; 60% of patients are diagnosed at younger 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% to 40%, explained, in part, by different subtypes among age groups, including the *BCR-ABL* fusion gene, which has a poor prognosis and is much less common in childhood ALL, as compared with adult ALL.

Disease genetics. Ph-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. (3) In ALL, the Ph is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is generally associated with acute lymphoblastic leukemia, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain of the BCR-ABL protein is the same as the kinase domain of the normal ABL protein. However, the abnormal BCR-ABL protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Treatment and response and minimal residual disease. Imatinib (Gleevec®) was originally developed to specifically target and inactivate the ABL tyrosine kinase portion of the BCR-ABL1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in "durable responses in [a] large proportion of the patients with a decreasing rate of relapse." (4) As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percent of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by six to 12 months after initial treatment with the TKI imatinib. (4) 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 (MRD). Among children with ALL who achieve a complete response (CR) by morphologic evaluation after induction therapy, approximately 25% to 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 polymerase chain reaction (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%. (5) Ig and T-cell receptor gene arrangement analysis is applicable for most 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% to 80% of patients achieving complete remission, significantly lower than that achieved in Ph-negative ALL. (6) The inclusion of TKIs to frontline induction chemotherapy has improved CR rates, exceeding 90%. (6)

<u>Resistance</u>

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. 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 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. (4, 7)

Structural studies of the ABL-imatinib complex have resulted in the design of second-generation ABL inhibitors, including dasatinib (Sprycel®) and nilotinib (Tasigna®), which were initially approved by the U.S. Food and Drug Administration (FDA) for treatment of patients resistant or intolerant to prior imatinib therapy. More recently,

trials of both agents in newly diagnosed chronic phase patients showed that both are superior to imatinib for all outcomes measured after one year of treatment, including CCyR (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis. (8, 9) Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. (10) On June 17, 2010, FDA approved nilotinib for the treatment of patients with newly-diagnosed chronic phase CML. Dasatinib was approved on October 28, 2010, for the same indication.

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, imatinib dose escalation from 400 mg to 800 mg daily, as tolerated or therapy change to an alternate second-generation TKI are all options. (4)

Molecular resistance. Resistance is most often explained at the molecular level by genomic instability associated with the creation of the abnormal *BCR-ABL1* gene, usually resulting in point mutations within the *ABL1* gene kinase domain that affects protein kinase-TKI binding. *BCR-ABL1* kinase domain (KD) point mutations account for 30% to 50% of secondary resistance. (7) At least 58 different KD mutations have been identified in CML patients. (11) The degree of resistance depends on the position of the mutation within the KD (i.e., active site) of the protein. Some mutations are associated with moderate resistance and are responsive to higher doses of TKIs, while other mutations may not be clinically significant. Two mutations, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance. The T315I mutation is relatively common at frequencies ranging from 4% to 19%, depending on the patient population; it is more common in patients with advanced phase CML than in patients with early chronic phase CML. (12-14)

Compared with imatinib, fewer mutations are associated with resistance to dasatinib or nilotinib. (15, 16) For example, Guilhot et al (17) and Cortes et al (18) 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* mutations. However, neither dasatinib nor nilotinib are effective against resistant clones with the T315I mutation, (11, 17) and new agents and treatment strategies are in development for patients with T315I resistance.

In a recent follow-up study of nilotinib by le Coutre et al, (19) 137 patients with accelerated phase CML were evaluated after 24 months. 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. (20) 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. (7)

Regulatory Status

The *BCR/ABL1* qualitative and quantitative genotyping tests, and ABL KD mutation tests, are not manufactured test kits and have not been reviewed by FDA. Rather, they are laboratory-developed tests (LDT), offered by clinical laboratories licensed under Clinical Laboratory Improvement Amendments (CLIA) for high-complexity testing.

Note that new BCR-ABL KD mutations also occur in about 80% to 90% of cases of acute lymphoblastic leukemia in relapse after TKI treatment, and in CML blast transformation.

Policy (Formerly Corporate Medical Guideline)

CML

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

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 (see Policy Guidelines) is considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance is considered **medically necessary** when there is inadequate initial response to treatment or any sign of loss of response (see Policy Guidelines); 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.

ALL

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

Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance is considered **medically necessary** when there is inadequate initial response to treatment or any sign of loss of response.

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

Policy Guideline

Diagnosis of CML and ALL

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 (RT-PCR), and reported results should be standardized according to the International Scale. For CML, testing is appropriate at baseline before the start of imatinib treatment and testing is appropriate every three months when the patient is responding to treatment. After a complete cytogenetic response is achieved, testing is recommended every three months for three years and then every three to six months thereafter. Without attainment of a complete cytogenetic response, continued

monitoring at three-month intervals is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib as well and will likely also be applied to bosutinib and ponatinib. 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 (TKIs) is defined as failure to achieve complete hematologic response at three months, only minor cytological response at six months or major (rather than complete) cytogenetic response at 12 months.

Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL who 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 one log increase in *BCR-ABL1* transcript ratio and therefore loss of major molecular response (MMR).

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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