

## Corporate Medical Policy

### BCR-ABL 1 Testing AHS – M2027

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### Description of Procedure or Service

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Chronic myeloid leukemia (CML) is a slowly-progressing cancer characterized by the clonal myeloproliferative expansion of pluripotent hematopoietic stem cells resulting from acquisition of the fusion oncogene BCR-ABL 1. Primarily occurring in adults, CML can change into a fast-growing and difficult to treat disease. Chronic myeloid leukemia accounts for 15% of all leukemias in adults (Cortes, Silver, Khoury, & Kantarjian, 2016).

*BCR-ABL 1* refers to the fusion gene which results from a reciprocal translocation that joins the ABL 1 gene from chromosome 9 to the BCR gene on chromosome 22, and is necessary for the development of CML. (Faderl et al., 1999) This reciprocal translocation also generates a shortened derivative chromosome 22, known as the Philadelphia (Ph) chromosome (Schrijver, Zehnder, & Cherry, 2018). The Ph chromosome is a diagnostic hallmark, present in 95% of people with CML and approximately 3%–5% children and 25%–40% adults with ALL (Leoni & Biondi, 2015).

Acute lymphoblastic leukemia (ALL) is an aggressive form of cancer resulting from the neoplastic transformation of lymphoid precursors characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and peripheral blood. Predominately a childhood disease, approximately 60% of cases were diagnosed in patients younger than 20 years of age (Pui, 2011).

#### Literature Review

CML was the first human malignancy in which a specific cytogenetic abnormality, “a minute chromosome”, could be linked to pathogenetic events of leukemogenesis (Nowell & Hungerford, 1960). The Philadelphia chromosome translocation (t(9;22)(q34;q11.2)), fuses the BCR gene from chromosome 22 with the ABL1 proto-oncogene from chromosome 9 in a head-to-tail manner (Schrijver et al., 2018) to form the transcriptionally active BCR/ABL fusion gene (Faderl et al., 1999). The fusion of BCR at the 5' side of SH3 in ABL, alters the tightly regulated function of SH3, disabling control over the tyrosine kinase. The resulting chimeric BCR/ABL protein has constitutively elevated tyrosine phosphokinase activity (Kurzrock, Kantarjian, Druker, & Talpaz, 2003) which activates a number of downstream signaling molecules including PI3K, MAPK, NFkB, RAS and STAT5 (Ren, 2005), disrupting cellular signal transduction pathways, and regulation of both apoptosis and cell proliferation (Warmuth et al., 1999), ultimately leading to factor-independent and leukemogenic cell growth (Faderl et al., 1999).

Detection of the Ph chromosome is the hallmark of CML and is found in up to 95 percent of patients (Leoni & Biondi, 2015). In approximately 5% of CML cases, the Ph chromosome cannot be detected, and BCR-ABL1 formation is attributed microscopically undetectable translocations or variant complex translocations involving a third chromosome (Schrijver et al., 2018). Independent of which other chromosomes are involved in variant translocations, the generation of the BCR/ABL fusion gene is necessary (Ankathil, Azlan, Dzarr, & Baba, 2018), as the 210-KDa fusion protein BCR-ABL is essential for initiation, maintenance and progression of CML (Ren, 2005).

The discovery of BCR-ABL-mediated pathogenesis of CML provided the rationale for the design of an inhibitory agent that targets BCR/ABL kinase activity (Ankathil et al., 2018). Protein kinases had been thought to be poor therapeutic targets because of their ubiquitous nature and crucial role in many normal physiologic processes (Kurzrock et al., 2003). The advent of imatinib mesylate (IM) by Novartis, demonstrated that designer kinase inhibitors could be specific (Kurzrock et al., 2003). IM binds to the inactive configuration domain of BCR/ABL kinase which competitively inhibits the adenosine triphosphate-binding site of the BCR/ABL oncoprotein and prevents the spurious phosphorylation of proteins involved in cell signal transduction (Ankathil et al., 2018). IM has shown striking activity in chronic myelogenous leukemia (Kurzrock et al., 2003). By directly targeting the BCR/ABL kinase, IM leads to durable cytogenetic response (CyR) and drastically improves overall survival (OS) rate to 88% after 5 years versus 57% from nonspecific treatment with hydroxyurea and interferon, with fewer side effects (Ankathil et al., 2018). Following the success of IM, other tyrosine kinase inhibitors (TKI) were developed. Commercially available TKIs for CML treatment are dasatinib, nilotinib, bosutinib and ponatinib. Other newer TKIs with higher potency and activity are also undergoing clinical development (Ankathil et al., 2018).

Depending on the precise breakpoints in the translocation and RNA splicing, different isoforms of BCR/ABL protein with different molecular weights (p185 BCR/ABL, p210 BCR/ABL and p230 BCR/ABL) can be generated (Ren, 2005). The p210 BCR/ABL isoform which is the hallmark of CML and also found in one-third of those with Ph-positive B cell ALL (Van Etten, 2018b) is generated from breakpoints in the major breakpoint cluster region (M-bcr) and the resulting fusion of exons 13 or 14 from BCR with exon 2 of ABL1 (Faderl et al., 1999). A second isoform, p190 BCR/ABL generated from breakpoints 5' of the M-bcr within a segment called the minor breakpoint cluster region (m-bcr) and the resulting fusion of exon 1 of BCR gene with exon 2 of ABL1 gene is associated with two-thirds of patients with Ph+ B-cell ALL (Clark et al., 1988; Fainstein et al., 1987) and a minority of patients with CML (Verma et al., 2009). A third isoform from a breakpoint 3' from the M-bcr region (u-bcr) resulting in the fusion of exon 19 of the BCR gene and exon 2 of the ABL1 gene is associated with the chronic neutrophilic leukemia variant and with thrombocytosis (Pane et al., 1996). These three isoforms display differential increased tyrosine kinase activity (Li, Ilaria, Million, Daley, & Van Etten, 1999; Lugo, Pendergast, Muller, & Witte, 1990) may in part account for the distinct leukemias associated with the different fusions, and may predict responsiveness to therapy with tyrosine kinase inhibitors (Van Etten, 2018a).

### Analytic validity

Molecular testing for the diagnosis of CML confirms typical findings in the blood and bone marrow by the demonstration of the Philadelphia chromosome, the BCR-ABL 1 fusion gene or the BCR-ABL 1 fusion mRNA, by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR) (Van Etten, 2018). Conventional cytogenetic karyotyping is no longer the diagnostic modality of choice due to its requirements for a highly skilled staff, culturing of cells, long turnaround time, and lower sensitivity (5-10%). Despite this, conventional cytogenetics are still the gold standard, and should be performed especially at diagnosis to detect additional clonal abnormalities (Yeung, Egan, & Radich, 2016). Fluorescence *in situ* hybridization (FISH) is more sensitive (0.1-5%) than karyotyping and can be performed on peripheral blood in addition to bone marrow and tissue. FISH is able to detect some very rare translocations not usually detectable by the vast majority of commercial and laboratory developed RT-PCR assays (Yeung et al., 2016). Quantitative RT-PCR is the most sensitive technique currently available (0.001-0.01%). To control for specimen quality of the RNA and to obtain semi-quantitative results, the quantity of BCR-ABL 1 transcript is determined in relation to an endogenous control gene, such as BCR, ABL 1, or GUSB (Yeung et al., 2016). As differences in laboratory technique and control genes can make it difficult to compare PCR values among laboratories, an international effort to standardize qRT-PCR results led to the development of the International Scale (IS) (Hughes et al., 2006) to provide a common approach for reporting the results of qRT-PCR. The IS is anchored to two values: (1) a standardized baseline value of 100% and (2) a standardized MMR value set at 0.1%, that is, a 3-log reduction from the standardized baseline (Bauer & Romvari, 2012). However, quantitative BCR-ABL 1 transcript levels on the IS vary widely at diagnosis as the ABL 1 standard produces unreliable results in samples with high BCR-ABL 1 transcript levels such as samples taken at or near diagnosis (Negrin & Schiffer, 2018).

## BCR-ABL 1 Testing AHS – M2027

Clinical trials of discontinuing TKI therapy after previously sustained undetectable BCR-ABL 1 transcripts have shown that more than half of patients show evidence of molecular relapse within six months indicating a population of expandable leukemic cells below the limit of detection of current methods (Mahon et al., 2010; Ross et al., 2013). Thus, there is continued research into more sensitive methods (Yeung et al., 2016).

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

### Policy

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**BCBSNC will provide coverage for BCR-ABL 1 testing when it is determined the medical criteria or reimbursement guidelines below are met.**

### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

### When BCR-ABL 1 testing is covered

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1. Qualitative or quantitative RT-PCR testing for identification of the BCR-ABL1 fusion gene transcript type is considered medically necessary for the differential diagnosis of CML or ALL
2. Quantitative testing on blood or bone marrow for the BCR-ABL 1 fusion gene transcript in individuals with CML, using the International Scale reporting convention, for patients prior to initiation or undergoing treatment with TKI therapy, is considered medically necessary:
  - a. As a baseline measurement prior to initiation of TKI therapy
  - b. Every 3 months after initiation of therapy after MMR (BCR-ABL 1 (IS) <1% (>0.1%-1%) has been achieved
  - c. Every 3 months for 2 years and every 3-6 months thereafter
  - d. If there is a 1-log increase in *BCR-ABL 1* transcript levels with MMR, repeat in 1-3 months
3. Quantitative testing on blood or bone marrow for the BCR-ABL1 fusion gene transcript in individuals with CML, using the International Scale reporting convention, for patients undergoing treatment discontinuation with TKI therapy and who remain in MMR after discontinuation of therapy, is considered medically necessary.
4. Evaluation of BCR-ABL kinase domain point mutations in patients with CML is considered medically necessary when:
  - a. There is insufficient response to TKI therapy, OR
  - b. There is loss of response to TKI therapy, OR
  - c. 1-log increase in BCR-ABL 1 transcript levels and loss of MMR
  - d. The disease progresses to accelerated or blast phase
5. Quantitative or qualitative testing on blood or bone marrow for the BCR-ABL 1 fusion gene transcript, including determination of transcript size (ie, p190 vs. p210), in individuals diagnosed with B-ALL, using the International Scale reporting convention, is considered medically necessary for optimal risk stratification, treatment planning, surveillance, and MRD assessment
6. Evaluation of BCR-ABL kinase domain point mutations in patients with ALL is considered medically necessary when there is relapsed or refractory disease in Ph positive ALL patients

### When BCR-ABL 1 testing is not covered

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Reimbursement is not allowed for testing of both bone marrow and blood for monitoring purposes.

**Policy Guidelines**

The National Comprehensive Cancer Network (NCCN, 2018b) recommendations for CML indicate:

Test	Recommendation
Quantitative RT-PCR (QPCR) using IS	<ul style="list-style-type: none"> <li>• At diagnosis</li> <li>• Every 3 months after initiating treatment. After BCR-ABL1 0.1%-&lt;1% (IS) has been achieved, every 3 months for 2 years and every 3-6 months thereafter</li> <li>• If there is 1-log increase in BCR-ABL1 transcript levels with MMR, QPCR should be repeated in 1-3 months</li> <li>• After Allogeneic HCT Complete cytogenetic response; every 3 months for 2 years, every 3-6 months thereafter.</li> </ul>
BCR-ABL kinase domain mutation analysis	<ul style="list-style-type: none"> <li>• Chronic phase                             <ul style="list-style-type: none"> <li>- Failure to reach response milestones</li> <li>- Any sign of loss of response (defined as hematologic or cytogenic relapse)</li> <li>- 1-log increase in BCR-ABL1 transcript levels and loss of MMR</li> </ul> </li> <li>• Disease progression to accelerated or blast phase</li> </ul>

The National Comprehensive Cancer Network(NCCN, 2018a) guidelines for ALL indicate:

Test	Recommendation
Quantitative RT-PCR (QPCR) using IS	<ul style="list-style-type: none"> <li>• Diagnosis. Genetic Characterization. Optimal risk stratification and treatment planning requires testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:                             <ul style="list-style-type: none"> <li>- Karyotyping of G-banded metaphase chromosomes</li> <li>- Interphase fluorescence in situ hybridization (FISH) testing including probes capable of detecting the major recurrent genetic abnormalities;</li> <li>- Reverse transcriptase polymerase chain reaction (RT-PCR) testing BCR-ABL1 in B-ALL (quantitative or qualitative) including determination of transcript size (ie, p190 vs p210).</li> </ul> </li> <li>• If BCR-ABL1 negative: encourage testing for gene fusions and mutations associated with Ph-like ALL (The Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2 or PDGFRB and mutations involving FLT3, IL7R, SH2B3, JAK1, JAK3, JAK2 (in combination with CRLF2 gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. The safety and efficacy of targeted agents in this population is an active area of research.)</li> </ul>

## BCR-ABL 1 Testing AHS – M2027

	<ul style="list-style-type: none"> <li>• Surveillance. Periodic BCR-ABL1 transcript-specific quantification (Ph+ ALL)</li> <li>• Minimal Residual Disease Assessment</li> <li>• Additional optional tests include:             <ul style="list-style-type: none"> <li>- additional assessment (array cGH) in cases of aneuploidy or failed karyotype</li> </ul> </li> </ul>
BCR-ABL kinase domain mutation analysis	Relapsed/ Refractory Disease

Guidelines from the European Society for Medical Oncology (A. Hochhaus et al., 2017):

Test	Baseline	Response	Monitoring
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, qRT-PCR (quantitative, BCR-ABL %)	No	Every 3 months	Every 4–6 weeks in first year after treatment discontinuation
Mutational Analysis	Only in accelerated or blast phase	No	Only in the case of failure

Guidelines from European LeukemiaNet(Baccarani et al., 2013):

Molecular testing must be performed by RQ-PCR on buffy-coat of more than 10 mL of blood, to measure BCR-ABL1 transcripts level, which is expressed as BCR-ABL1% on the IS. RQ-PCR should be performed every 3 months until a MMR (MR<sup>3.0</sup> or better) is achieved, then every 3 to 6 months. It is not possible to assess achievement of MMR if the IS is not available. However, if transcripts are not detectable with a threshold sensitivity of 10<sup>-4</sup>, this is likely in the range of MMR or below. It is important to realize that it is not unusual for PCR results to fluctuate up and down over time, in part because of laboratory technical reasons. If transcript levels have increased >5 times in a single follow-up sample and MMR was lost, the test should be repeated in a shorter time interval, and patients should be questioned carefully about compliance.

If cytogenetics is used, it must be performed by CBA of marrow cell metaphases, counting at least 20 metaphases, at 3, 6, and 12 months until a CCyR is achieved, and then every 12 months. CBA can be substituted by FISH on blood cells only when a CCyR has been achieved.

In case of warning, it is recommended to repeat all tests, cytogenetic and molecular, more frequently, even monthly.

In case of treatment failure or of progression to AP or BP, cytogenetics of marrow cell metaphases, PCR, and mutational analysis should be performed.

### **The 2016 World Health Organization classification of myeloid neoplasms and acute leukemia**

In the recent revision of the 4<sup>th</sup> edition on Classification of Tumors of Hematopoietic and Lymphoid Tissues, World Health Organization (WHO) incorporated new molecular genetic findings and clinical data into its classification of acute leukemias(Arber et al., 2016).

## BCR-ABL 1 Testing AHS – M2027

They state that : “With regard to chronic myeloid leukemia (CML), BCR-ABL1<sup>+</sup>, most cases of CML in chronic phase can be diagnosed from peripheral blood (PB) findings combined with detection of t(9;22)(q34.1;q11.2) or, more specifically, *BCR-ABL1* by molecular genetic techniques. However, a bone marrow (BM) aspirate is essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease. In the era of tyrosine-kinase inhibitor (TKI) therapy, newly diagnosed patients may have a nearly normal lifespan, but regular monitoring for *BCR-ABL1* burden and for evidence of genetic evolution and development of resistance to TKI therapy is essential to detect disease progression.”

They also introduced a provisional classification of ALL: B-ALL with translocations involving tyrosine kinases or cytokine receptors (“BCR-ABL1-like ALL”).

“This newly recognized entity is assuming increasing importance because of its association with an adverse prognosis and responses of some cases to TKI therapies; however, it has been difficult to define in the clinical setting. It was originally described separately by different groups who demonstrated a series of cases of poor-prognosis childhood ALL with gene expression profiles similar to those seen in cases of ALL with BCR-ABL1, though different algorithms applied to the same sets of cases did not classify all cases the same way.”

“The cases with translocations involving tyrosine kinase genes involve many different genes including ABL1 (with partners other than BCR), as well as other kinases including ABL2, PDGFRB, NTRK3, TYK2, CSF1R, and JAK2. Over 30 different partner genes have been described. Some patients, especially those with EBF1-PDGFRB translocations, have shown remarkable responses to TKI therapy, even after failing conventional therapy.”

### **The 2017 College of American Pathologists and American Society of Hematology**

Following recent progress in molecular genetic findings and 2016 WHO classification of acute leukemias, the College of American Pathologists (CAP) and the American Society of Hematology (ASH) have formed an expert panel to review and establish guidelines for appropriate laboratory testing (Arber et al., 2017). The published guideline provides twenty-seven guideline statements ranging from recommendations on what testing is appropriate for the diagnostic and prognostic evaluation of leukemias to where the testing should be performed and how results should be reported.

For pediatric patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(12;21)(p13.2;q22.1); ETV6- RUNX1, t(9;22)(q34.1;q11.2); BCR-ABL1, KMT2A(MLL) translocation, iAMP 21, and trisomy 4 and 10 is performed. Strong Recommendation

For adult patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2) ; BCR-ABL1 is performed. In addition, testing for KMT2A (MLL) translocations may be performed. Strong Recommendation for testing for t (9;22) (q34.1;q11.2) and BCR-ABL1; Recommendation for testing for KMT2A (MLL) translocations may be performed.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81170, 81206, 81207, 81208, 81401, 0016U, 0040U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

### Scientific Background and Reference Sources

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## BCR-ABL 1 Testing AHS – M2027

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## BCR-ABL 1 Testing AHS – M2027

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Medical Director review 8/2019

Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

**For Policy Titled: BCR-ABL 1 Testing**

Medical Director review 7/2020

## Policy Implementation/Update Information

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**For Policy Titled: BCR-ABL 1 Testing for Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia**

## BCR-ABL 1 Testing AHS – M2027

- 1/1/2019 New policy developed. BCBSNC will provide coverage for BCR-ABL1 testing for chronic myeloid leukemia and lymphoblastic leukemia when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 10/1/19 Under “When Covered” section: added 2. C. “Every 3 months for 2 years and every 3-6 months thereafter.” Deleted 2.D. “After allogeneic HCT complete cytogenetic response, every 3 months.” Deleted coding table from Billing/Coding section and deleted CPT code 81403; added PLA codes: 0016U, 0040U for effective date 10/1/19. Medical Director review 8/2019. (lpr)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
- 5/26/20 Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statement. (lpr)

### **For Policy Titled: BCR-ABL 1 Testing**

- 7/28/20 Reviewed by Avalon Q2 2020 CAB. Updated references. **Policy Title changed from: BCR-ABL 1 Testing for Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia to: BCR-ABL 1 Testing.** Medical Director review 7/2020. (lpr)

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