

## Corporate Medical Policy

### BCR-ABL 1 Testing AHS – M2027

**File Name:** bcr\_abl\_1\_testing  
**Origination:** 1/1/2019  
**Last Review:** 8/2022

#### Description of Procedure or Service

---

Oncogenesis can result when specific genes or regions of chromosomes are translocated elsewhere within the genome. *BCR-ABL1*, for example, refers to the fusion gene resulting from a reciprocal translocation that joins the *ABL1* gene from chromosome 9 to the *BCR* gene on chromosome 22 and is necessary for the development of chronic myeloid leukemia (CML) (Van Etten, 2021). This reciprocal translocation also generates a shortened derivative chromosome 22, known as the Philadelphia (Ph) chromosome (Schrijver & Zehnder, 2020). The Ph chromosome is a diagnostic hallmark, present in 95% of people with CML and approximately 3%–5% children and 25%–40% adults with acute lymphoblastic leukemia (ALL) (Leoni & Biondi, 2015), 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 (PDQ, 2019). Predominately a childhood disease, approximately 60% of cases were diagnosed in patients younger than 20 years of age (Pui, 2011).

#### **Related Policies:**

Serum Tumor Markers for Malignancies AHS-G2124  
Genetic Testing for Acute Myeloid Leukemia AHS-M2062  
Genetic Cancer Susceptibility Panels Using Next Generation Sequencing AHS-M2066  
Mutation Analysis in Myeloproliferative Neoplasms AHS-M2101  
General Genetic Testing, Germline Disorders AHS-M2145  
General Genetic Testing, Somatic Disorders AHS-M2146

***\*\*\* 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

---

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

#### Benefits Application

---

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

---

1. Qualitative or quantitative reverse transcription polymerase chain reaction (RT-PCR) testing for identification of the *BCR-ABL1* fusion gene transcript type is considered medically necessary for the differential diagnosis of chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL).
2. Prior to initiation or while undergoing treatment with TKI therapy, quantitative testing on blood or bone marrow for the *BCR-ABL1* fusion gene transcript in individuals with CML, using the

## BCR-ABL 1 Testing AHS – M2027

International Scale reporting convention, is considered medically necessary with the following frequencies:

- a. Every 3 months after initiation of therapy until major molecular response (MMR)(BCR-ABL1 (IS) <1% (>0.1%-1%) has been achieved
- b. Every 3 months for 2 years and every 3-6 months thereafter
- c. If there is a 1-log increase in *BCR-ABL1* transcript levels with MMR, repeat in 1-3 months.
3. For patients undergoing treatment discontinuation with TKI therapy and who remain in MMR after discontinuation of therapy, quantitative testing on blood or bone marrow for the *BCR-ABL1* fusion gene transcript in individuals with CML, using the International Scale reporting convention, 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 failure to reach response milestones; OR
  - b. There is any sign of loss of hematologic response; OR
  - c. There is any sign of loss of complete cytogenetic response (CCyR) or its molecular response correlate defined as an increase in *BCR-ABL1* transcript to 1%; OR
  - d. 1-log increase in *BCR-ABL1* transcript levels and loss of MMR; OR
  - e. The disease progresses to accelerated or blast phase.
5. Quantitative or qualitative testing on blood or bone marrow for the *BCR-ABL1* fusion gene transcript, including determination of transcript size (ie, p190 vs. p210), in individuals diagnosed with B-cell (B-ALL), using the International Scale reporting convention, is considered medically necessary for optimal risk stratification, treatment planning, surveillance, and MRD assessment.
6. When there is relapsed or refractory disease in Philadelphia chromosome positive (Ph+) ALL patients, evaluation of *BCR-ABL* kinase domain point mutations is considered medically necessary.

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

---

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

### Policy Guidelines

---

A translocation occurs when specific genes or regions of a chromosome are moved from one chromosome to another. Several human diseases are caused by translocations. In particular, a few types of leukemia (such as acute myeloid leukemia and chronic myeloid leukemia) are known to occur due to spontaneous translocations.

Chronic myeloid leukemia (CML) was the first human malignancy in which a specific chromosomal defect, known as the minute or Philadelphia (Ph) chromosome, could be linked to pathogenetic events of leukemogenesis (Nowell & Hungerford, 1960). The Ph chromosome translocation (t(9;22)(q34;q11.2)) fuses the breakpoint cluster region protein (*BCR*) gene from chromosome 22 with the Abelson murine leukemia viral oncogene homolog 1 (*ABL1*) proto-oncogene from chromosome 9 in a head-to-tail manner to form the transcriptionally active *BCR-ABL* fusion gene (Schrijver & Zehnder, 2022). The fusion of *BCR* at the 5' side in *ABL* alters the tightly regulated function of the Src homology 3 (SH3) domain, disabling control over the tyrosine kinase enzyme. The resulting chimeric BCR-ABL protein has constitutively elevated tyrosine phosphokinase activity (Kurzrock, Kantarjian, Druker, & Talpaz, 2003) that activates a number of downstream signaling molecules, including PI3K, AKT, JNK, RAS and STAT5 (Ren, 2005). This then disrupts cellular signal transduction pathways, leading to issues in the regulation of both apoptosis and cell proliferation (Warmuth, Danhauser-Riedl, & Hallek, 1999), ultimately leading to factor-independent and leukemogenic cell growth (Van Etten, 2021).

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 to microscopically undetectable translocations or variant complex translocations involving a third chromosome (Schrijver & Zehnder, 2022). Independent of which other chromosomes are

## BCR-ABL 1 Testing AHS – M2027

involved in variant translocations, the generation of the *BCR-ABL* fusion gene is the “fundamental cause of Ph-positive leukemias” (Van Etten, 2021), as the 210-KDa fusion protein BCR-ABL is essential for initiation, maintenance, and progression of CML (Ren, 2005). Testing for BCR-ABL1 detects both the Ph chromosome and fusion gene or its transcripts. The BCR-ABL1 transcript is the RNA copy made by the cell.

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+ B-cell acute lymphoblastic leukemia (ALL), is generated from breakpoints in the major breakpoint cluster region (M-bcr) and results in the fusion of exons 13 or 14 from *BCR* with exon 2 of *ABL1* (Van Etten, 2020). A second isoform, p190 BCR-ABL, is 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 and a minority of patients with CML (Van Etten, 2021; 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. These three isoforms display differential increased tyrosine kinase activity that may in part account for the distinct leukemias associated with the different fusions; moreover, they may predict responsiveness to therapy with tyrosine kinase inhibitors (Van Etten, 2021).

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, which eventually led to the creation of tyrosine kinase inhibitors (TKIs) (Negrin & Schiffer, 2019). Protein kinases had been thought to be poor therapeutic targets because of their ubiquitous nature and crucial role in many normal physiologic processes. The development 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, competitively inhibiting the adenosine triphosphate-binding site of the BCR-ABL oncoprotein (Negrin & Schiffer, 2019). IM has shown striking activity in chronic myelogenous leukemia (Kurzrock et al., 2003). By directly targeting the BCR-ABL kinase, IM leads to inhibition of cell proliferation and tumor formation without induction of apoptosis. IM has also been estimated to lead to a 92%-98% reduction of CML colonies without inhibiting normal colony growth (Negrin & Schiffer, 2019). Following the success of IM, other TKIs were developed. Commercially available TKIs for CML treatment are imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. Other newer TKIs with higher potency and activity are also being produced to inhibit additional signaling pathways or overcome resistance (Negrin & Schiffer, 2019).

Molecular monitoring allows the detection of low levels of residual leukemia cells and provides important prognostic information for CML patients (Latremouille-Viau et al., 2017) as molecular responses are predictive of patient outcomes (Bauer & Romvari, 2012). Molecular monitoring during treatment with TKI helps determine whether a patient is responding optimally to treatment, helps identify those at risk of progression, and provides evidence regarding the need to reassess treatment or initiate second-line therapy (Hughes et al., 2006).

### ***Treatment Failure***

Despite the excellent efficacy and improved clinical responses, development of resistance in a significant proportion (30-35%) of CML patients on IM therapy has emerged (Ankathil, Azlan, Dzarr, & Baba, 2018). Mutations in the BCR-ABL kinase domain have been identified as the major contributory factor in resistance (O'Hare, Eide, & Deininger, 2007). Hence, *BCR-ABL* mutation analysis is an important component of disease monitoring in patients with clinical signs of resistance (Soverini et al., 2011). Mutation analysis is routinely performed using Sanger sequencing (SS) which is a method of DNA sequencing. However, next-generation sequencing (NGS), a high-throughput approach to DNA sequencing, has recently been utilized as a more sensitive and effective testing method. Compared to SS, NGS is able to detect a lower frequency and earlier existence of mutations, which allows for more effective therapeutic tailoring (Ankathil et al., 2018). *BCR-ABL* mutation screening is clinically relevant to identify CML patients who are more likely to have a poor outcome due to the disease. This is because mutations in different regions of the BCR-ABL tyrosine kinase domain lead to different levels of resistance (Smith et al., 2006) and the type of mutation can

## BCR-ABL 1 Testing AHS – M2027

potentially indicate whether second- or third-generation TKIs or alternative therapeutic strategies should be given to IM-resistant patients (Milojkovic & Apperley, 2009). However, *BCR-ABL* tyrosine kinase domain (TKD) mutations cannot always explain IM resistance; therefore, additional resistance mechanisms should be addressed. Reduced bio-availability of IM in leukemic cells clonal chromosomal evolution, BCR-ABL amplification, pharmacogenomic variations, as well as activation of signaling shortcuts, have all been implicated in drug resistance (Ankathil et al., 2018).

### *Analytical Validity*

Molecular testing for the diagnosis of CML confirms typical findings in the blood and bone marrow by the demonstration of the Ph chromosome, the *BCR-ABL1* fusion gene or the BCR-ABL1 fusion mRNA. Molecular testing techniques include conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis and reverse transcription polymerase chain reaction (RT-PCR) (Van Etten, 2020). 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). FISH is more sensitive (0.1-5%) than karyotyping and can be performed on peripheral blood in addition to bone marrow and tissue. FISH can detect certain very rare translocations not usually detectable by the vast majority of commercial and laboratory-developed RT-PCR assays, but FISH is highly specific to the targeted region and may miss other chromosomal changes. Quantitative RT-PCR is the most sensitive technique currently available (0.001-0.01% sensitivity).

The quantity of the BCR-ABL1 mRNA transcript is determined in relation to an endogenous control gene (such as *BCR*, *ABL1*, or *GUSB*) to control for specimen quality of the RNA and to obtain semi-quantitative results (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 quantitative RT-PCR (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 major molecular response (MMR) value set at 0.1%, that is, a 3-log reduction from the standardized baseline (Bauer & Romvari, 2012). However, quantitative BCR-ABL1 transcript levels on the IS vary widely at diagnosis as the ABL1 standard produces unreliable results in samples with high BCR-ABL1 transcript levels, such as samples taken at or near diagnosis (Schiffer & Atallah, 2020).

Clinical trials of discontinuing TKI therapy after previously sustained undetectable BCR-ABL1 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).

On July 22, 2016 the FDA approved the QuantideX qPCR BCR-ABL IS Kit as an *in vitro* nucleic acid amplification test for the quantitation of BCR-ABL1 and ABL1 transcripts in total RNA from whole blood of diagnosed t(9;22) positive Chronic Myeloid Leukemia (CML) patients expressing BCR-ABL1 fusion transcripts type e13a2 and/or e14a2 as a class II device with special controls (FDA, 2016). Brown et al. (2019) performed a study to describe the analytical validation of this kit. They were able to find that “the test has a limit of detection of MR molecular response] 4.7 (0.002% IS) and a linear range from MR0.3 (50%IS) to MR4.7 (0.002%IS) for both Major transcripts. Single-site and multisite precision studies demonstrated a maximum SD of 0.13 MR (30% CV within the assay range between MR0.7 and MR3.7).”

Amin compared the results of using the endpoint fluorescence (EPF) method and quantitative real-time polymerase chain reaction (QPCR) to monitor CML patients in treatment. One hundred and fifty~~450~~ blood samples from 30 CML patients were analyzed using EPF and qPCR simultaneously to detect BCR-ABL transcript mRNA. One hundred and seventeen of 150 samples (78%) were positive for the transcript whereas 33 of 150 samples (22%) were negative for the transcript at various stages of treatment using both methods. There both had strong linear negative correlations between the cycle threshold and relative fluorescence unit values with  $P < .0001$  at 0, 3, 6, 9, and 12 months of treatment. The authors conclude that

## BCR-ABL 1 Testing AHS – M2027

“EPF is a simple method to detect *BCR-ABL* mRNA expression during treatment with comparable results to QPCR” (Amin & Ahmed, 2021).

### *Clinical Utility and Validity*

Lima et al. (2011) “compared simultaneously obtained bone marrow (BM) cytogenetics (CTG), peripheral blood (PB) and BM fluorescence in situ hybridization (FISH), and quantitative real-time polymerase chain reaction (Q-PCR) for BCR-ABL1 in monitoring response to treatment with tyrosine kinase inhibitors and homoharringtonine (HHT) in patients with chronic myeloid leukemia.” A total of 112 PB and BM FISH samples were obtained along with 132 qPCR samples. The authors found that “excellent correlations ( $r$ ) were observed between PB and BM FISH ( $r = 0.95$ ) and PB and BM Q-PCR ( $r = 0.87$ ), as well as BM CTG and PB FISH ( $r = 0.89$ ) and PB Q-PCR ( $r = 0.82$ ).” Conclusions stated that “This correlation was not affected by the presence of the Ph<sup>+</sup> variant or additional chromosomal abnormalities, the presence of ABL1 kinase domain mutations, phase of the disease, or treatment (Lima et al., 2011).”

Kantarjian et al. (2003) evaluated the response and minimal residual disease (MRD) of 180 patients with Ph<sup>+</sup> chronic-phase, treated with imatinib mesylate by quantitative competitive PCR (QC-PCR). The MRD describes the low number of cancer cells still present in the body after treatment. The authors reported that “the median QC-PCR values for cytogenetic response categories were: no response (Ph, >90%), 36%; minor response (Ph, 35-90%), 22%; partial response (Ph, 1-34%), 7.3%; complete response (Ph, 0%), 0.89%. There was good correlation between cytogenetic and QC-PCR studies ( $P < 0.001$ ;  $r = 0.92$ ) and good concordance between QC-PCR values (>10%, 2-10%, and <2%) and cytogenetic response categories (none, minor, partial, complete) with a concordance rate of 66%, and major discordance of only 10%. Of 170 samples in complete cytogenetic response, 21% still had QC-PCR values of >10%, and 53% had QC-PCR values of <1%. There was excellent concordance between blood and marrow QC-PCR values ( $r = 0.965$ ;  $P < 0.01$ ; concordance rate, 88%; major discordance, 0%).” The authors concluded that “QC-PCR studies provide a useful tool to monitor patients with CML on imatinib mesylate therapy (Kantarjian et al., 2003).”

Goldberg et al. (2013) performed a retrospective chart review of 402 chronic myelogenous leukemia in chronic phase (CML-CP) patients on first-line imatinib therapy analyzing the impact of molecular monitoring frequency on the risk of progression and progression-free survival. The researchers found that “Compared to patients with no qPCR monitoring, those with 3-4 qPCR tests per year had a lower risk of progression (HR = 0.085;  $p = 0.001$ ) and longer PFS [progression free survival] (HR = 0.088;  $p = 0.001$ ) after adjusting for potential confounders, as did those patients with 1-2 qPCR tests per year (both  $p < 0.02$ ) (Goldberg et al., 2013).”

Guerin, Chen, Dea, Wu, and Goldberg (2014a) performed a retrospective cohort study of 1205 diagnosed CML-CP patients obtained from two large US administrative claims databases. The researchers aimed to analyze the frequency of molecular monitoring via qPCR and medication adherence. Approximately 41% of patients had no qPCR tests, 31.9% had 1-2 tests, and 27.1% had 3-4 tests. Adherence to therapy was calculated by “medication possession ratio” (MPR) and “proportion of days covered” (PDC). The 3-4 test cohort was found to have higher adherence to therapy (higher MPR and PDC) than the 0 and 1-2 test cohort. The authors concluded that “frequent molecular monitoring (3-4 times per year as recommended in current guidelines) is associated with greater TKI treatment adherence for patients diagnosed with CML” (Guerin et al., 2014a).

Guerin, Chen, Dea, Wu, and Goldberg (2014b) also used a retrospective US claims administrative database to analyze the economic impact of qPCR testing in CML patients on first-line TKIs during the initial 12-months of treatment. A total of 41% of patients had no qPCR tests, 31.9% had 1-2 tests, and 27.1% had 3-4 tests. However, patients that had 3-4 tests also had 44% fewer inpatient admissions than patients with 0 tests, leading to \$5663 in all-cause savings for the 3-4 test group. Overall, the medical service cost savings was calculated to be \$5997 for the 3-4 test group. The investigators concluded that “Among CML patients in two large claims databases, nearly three-quarters did not receive adequate molecular monitoring per published guidelines. Those who were more frequently monitored incurred lower medical service costs, with the majority of the difference in costs being related to disease progression. These findings underscore the clinical and economic values of molecular monitoring in CML (Guerin et al., 2014b).”

## BCR-ABL 1 Testing AHS – M2027

More recently, Latremouille-Viau et al. (2017) studied direct and indirect effects of qPCR test frequency using multivariate regression models. The authors created an economic model to evaluate the effect of qPCR test frequency on CML treatment in various clinical scenarios and reported their results as the increase from one qPCR test to two. The researchers found that increasing qPCR tests by one led to fewer inpatient days, fewer ER visits, more outpatient service days, and increased TKI adherence. The authors concluded that increasing the qPCR tests from 1 to 2 was associated with a cost savings of \$2918 per patient per year (Latremouille-Viau et al., 2017).

Yu, Cui, He, Jing, and Wang (2017) conducted a review on the challenges for standardizing the measurement of *BCR-ABL1*. Though using the IS and conversion factors (CFs) were critical in facilitating "interlaboratory comparison and the process of standardization," the lack of more comprehensive reference materials, including other DNA "atypical subtypes relevant to minor patients with CML and other hematological disorders remain additional attention." This could lead to delays in diagnosis "when a screening test for the common e13a2 and e14a2 transcripts is negative. In other cases, the lack of precise response data that can be aligned with molecular response targets on the *BCR-ABL1* International Scale (*BCR-ABL1*<sup>IS</sup>) might limit the clinician's capacity to detect sub-optimal response or impending resistance and alter treatment accordingly" (Pagani et al., 2020).

In understanding the clinical application of *BCR-ABL1* measurement, Yu et al. (2017) also noted that the IRIS (International Randomized Study of Interferon and STI571) trial made successful use of *BCR-ABL1* (IS) to observe patient response to imatinib: "At 6 months, patients who obtained a *BCR-ABL1* (IS) <10% had an EFS [event-free survival] rate >85% at 84 months, much higher than those who did not... Patients who had loss of CCyR [complete cytogenetic response], MMR [major molecular response], or increasing levels of *BCR-ABL1* had increased rate of progression to AP/BC [accelerated phase/blast crisis]." Reviews of the IRIS study recognized how *BCR-ABL1* became critical for quantifying CCyR and MMR during treatment (Yu et al., 2017).

D'Adda et al. (2019) evaluated the effect of the *BCR-ABL* transcript on efficacy of TKIs. The *BCR-ABL1* fusion gene may cause CML pathogenesis due to several breakpoints; the most common occur around exon 13 and 14 of the *BCR* gene and cause the formation of e13a2 and e14a2 transcripts (Greenfield et al., 2019). Out of 173 sampled patients, 67 had the e13a2 transcript, and 106 had the e14a2 version. The patients with the e14a2 version were more likely to achieve a deep molecular response to TKIs (sustained or otherwise). After 68 months, the sustained deep molecular response (sDMR) rate was 39.6% for e14a2 patients compared to 19.6% for e13a2 patients. Overall, the maximum rate of sDMR for e13a2 patients was 37%, after 60 months. Furthermore, only 2 patients (3%) with the e13a2 transcript achieved treatment-free remission (TFR) whereas 25 of e14a2 patients achieved TFR (23%) (D'Adda et al., 2019).

Dulucq et al. (2019) researched the impact of a second *BCR-ABL1* transcript decline rate on CML-CP patients treated with imatinib. The researchers analyzed the *BCR-ABL1* transcript decline rate from the three to six-month period after beginning treatment; *ABL1* was used as an internal control gene. A total of 216 CML-CP patients treated with 400 mg of imatinib participated in this study (Dulucq et al., 2019). Data was sorted into the following categories: event-free (EFS), failure-free (FFS), progression-free (PFS), and overall survivals (OS). The researchers found that the "percentage of *BCR-ABL1* decline from month 3 to month 6 was significantly linked to the EFS and the FFS ( $p < 0.001$ )"; further, the data also showed that "Patients with a decrease below 67% have worse EFS and FFS as compared to those having a higher decrease ( $p < 0.001$ ) (Dulucq et al., 2019)."

Pagani et al. (2020) comments on how genomic DNA Q-PCR, a highly sensitive assay, was able to detect "a case of e19a2 CML with imatinib in association with a T315I kinase domain mutation" that required asciminib to elicit a "deep molecular response determined by patient-specific genomic DNA PCR." This demonstrates the continued, seemingly ubiquitous clinical utility of DNA Q-PCR in testing *BCR-ABL1* transcripts for treatment response patients with CML despite this case being of an unconventional transcript (Pagani et al., 2020).

## BCR-ABL 1 Testing AHS – M2027

In a retrospective study, Yang reported the clinical significance of *BCR-ABL1* mutations in patients with Philadelphia chromosome-positive CML who underwent allogeneic hematopoietic cell transplantation. Of 315 patients in this study, point mutations were detected in 152 patients. One hundred and one of these 152 patients (66%) had T315I mutations and 51 had mutations other than T315I. The patients were followed 38 months later and overall survival at 3 years was worse in patients with the mutations than the non-mutation group, especially in the chronic phase of CML. Overall survival in the non-T315I group was significantly worse than that in the no-mutation group. The authors conclude that "mortality risk was significantly higher in patients with the BCR-ABL1 mutation than in patients without the mutation" (Tachibana et al., 2022).

### Guidelines and Recommendations

#### National Comprehensive Cancer Network (NCCN)

The NCCN's recommendations for CML include the following table (NCCN, 2022b)

Test	Recommendation
QPCR using IS	<ul style="list-style-type: none"> <li>• At diagnosis</li> <li>• Every 3 months after initiating treatment. After <i>BCR-ABL1</i> (IS) &lt;1%<sup>2</sup> (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 <i>BCR-ABL1</i> transcript levels with MMR, qPCR should be repeated in 1-3 months</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 hematologic response</li> <li>- Any sign of loss of CCyR or its molecular response correlate defined as an increase in BCR-ABL1 transcript to 1%.</li> <li>- 1-log increase in <i>BCR-ABL1</i> transcript levels and loss of MMR</li> </ul> </li> <li>• Disease progression to accelerated or blast phase<sup>3</sup></li> </ul>
Bone Marrow Cytogenetics <sup>1</sup>	<ul style="list-style-type: none"> <li>• At diagnosis</li> <li>• Failure to reach response milestones</li> <li>• Any signs of loss of hematologic response</li> <li>• Any sign of loss of CCyR or its molecular response correlate defined as an increase in <i>BCR-ABL1</i> transcript to 1%.</li> </ul>

<sup>1</sup>FISH has been inadequately studied for monitoring response to treatment.

<sup>2</sup>CCyR correlates with *BCR-ABL1* (IS) ≤1%.

<sup>3</sup>Consider myeloid mutation panel to identify BCR-ABL1-independent resistance mutations in patients with no BCR-ABL1 kinase domain mutations

The NCCN (2021b) also states that for the diagnosis and workup of CML-1:

- "Initial evaluation should consist of a history and physical exam, including palpation of spleen, complete blood count (CBC) with differential, chemistry profile, and hepatitis B panel. Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts at baseline are recommended to confirm the diagnosis of CML.
- Bone marrow cytogenetics should be done at initial workup to detect additional chromosomal abnormalities in Ph-positive cells (ACA/Ph<sup>+</sup>), also known as clonal cytogenetic evolution. If bone marrow evaluation is not feasible, fluorescence *in situ* hybridization (FISH) on a peripheral blood specimen with dual probes for *BCR* and *ABL1* genes is an acceptable method to confirm the diagnosis of CML."

## BCR-ABL 1 Testing AHS – M2027

- Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable *BCR-ABL1* mRNA transcripts. qPCR for the detection of atypical *BCR-ABL1* transcripts should be considered if there is discordance between FISH and qPCR results” (NCCN, 2022b).

### Acute Lymphoblastic Leukemia (ALL)

Regarding ALL, the NCCN (NCCN,2022a) recommends testing of marrow or peripheral blood lymphoblasts using various techniques. The guidelines state the following:

“The diagnosis of ALL generally requires demonstration of  $\geq 20\%$  bone marrow lymphoblasts, upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- Morphologic assessment of Wright-Giemsa-stained bone marrow aspirate smears, and H&E-stained core biopsy and clot sections
- Comprehensive flow cytometric immunophenotyping
- Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease analysis
- Karyotyping of G-banded metaphase chromosomes

Optimal risk stratification and treatment planning requires testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:

- Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities;
- 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).
- Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended.
- Assessment with chromosomal microarray (CMA)/array cGH in cases of aneuploidy or failed karyotype”

### Pediatric Acute Lymphoblastic Leukemia (PEDALL)

In 2019, the NCCN first issued a new set of guidelines titled *Pediatric Acute Lymphoblastic Leukemia*. These guidelines have been updated since the original issue date, with the most recent revision having been on October 1, 2021. For PEDALL, the NCCN encourages “testing for gene fusions and mutations associated with *BCR-ABL1*-like (Ph-like) ALL (NCCN, 2021).” The guidelines also state that “The *BCR-ABL1*-like (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 *CRLF2*, *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene functions). Testing of these abnormalities at diagnosis may aid in risk stratification (NCCN, 2021).”

The NCCN table of potentially actionable or prognostic mutations for PEDALL is given below (NCCN, 2021):

Risk Groups	Genetics
Favorable risk features	High hyperdiploidy (51 – 67 chromosomes) <ul style="list-style-type: none"> <li>Trisomy of chromosomes 4, 10, and 17 are among trisomies that have the most favorable outcome</li> </ul>
	Cryptic t(12;21)(p13;q22): <ul style="list-style-type: none"> <li><i>ETV6-RUNX1</i> fusion</li> </ul>



## BCR-ABL 1 Testing AHS – M2027

Unfavorable risk features	Hypodiploidy (<44 chromosomes)
	<i>KMT2Ar</i> (t[4;11] or others)
	t(9;22)(q34;q11.2)
	<ul style="list-style-type: none"> <li>• <i>BCR-ABL1</i></li> </ul>
	<i>BCR-ABL1</i> -like (Ph-like) ALL
	<ul style="list-style-type: none"> <li>• JAK-STAT <ul style="list-style-type: none"> <li>○ <i>CRLF2r</i></li> <li>○ <i>EPORr</i></li> <li>○ <i>JAK1/2/3r</i></li> <li>○ <i>TYK2r</i></li> <li>○ <i>SH2B3</i> mutations</li> <li>○ <i>IL7R</i> mutations</li> <li>○ <i>JAK1/2/3</i> mutations</li> </ul> </li> <li>• ABL class rearrangements of: <ul style="list-style-type: none"> <li>○ <i>ABL1</i></li> <li>○ <i>ABL2</i></li> <li>○ <i>PDGFRA</i></li> <li>○ <i>PDGFRB</i></li> <li>○ <i>FGFR</i></li> </ul> </li> <li>• Other <ul style="list-style-type: none"> <li>○ <i>NTRKr</i></li> <li>○ <i>FLT3r</i></li> <li>○ <i>LYNr</i></li> <li>○ <i>PTK2Br</i></li> </ul> </li> </ul>
	t(17;19)
<ul style="list-style-type: none"> <li>• <i>TCF3-HLF</i> fusion</li> </ul>	
Intrachromosomal amplification of chromosome 21 ( <i>iAMP21</i> )	
Alterations of <i>IZKF1</i> <sup>†</sup>	
<p>† NOTE: The NCCN states, “Emerging evidence suggests <i>DUX4r</i> ALL is favorable. Additionally in cases of <i>DUX4r</i>, <i>IZKF1</i> alterations do not confer poor prognosis (NCCN, 2021).”</p>	

### European LeukemiaNet

The European LeukemiaNet (a publicly funded research network) convened an expert panel to evaluate recommendations for treating CML. These guidelines were published in 2013 and were recently updated in 2020.

In 2013, Baccarani et al. (2013) published the following guidelines on behalf of the European LeukemiaNet:

- “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 major molecular response (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 International Scale (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 chromosome banding analysis (CBA) of marrow cell metaphases, counting at least 20 metaphases, at 3, 6, and 12 months until a complete

## BCR-ABL 1 Testing AHS – M2027

cytogenetic response (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.”

In 2020, Hochhaus et al. (2020) published the following guidelines on behalf of the European LeukemiaNet:

- “Good quality molecular testing is now available worldwide replacing cytogenetic monitoring in most situations and obviating the need for bone marrow aspirations. If a change in therapy is under consideration because of inadequate response or disease progression (drug resistance), a bone marrow aspiration is recommended to assess for cytogenetic clonal evolution. *BCR-ABL1* KD-mutation analysis should also be done in such circumstances.
- Treatment should be managed in cooperation with a specialized referral center where there is rapid access to quality-controlled, reliable tests including chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH) for specific cases, and quantitative reverse transcriptase polymerase chain reaction (qPCR) with mutation analysis (Sanger or next generation sequencing, NGS).
- Cytogenetics should be performed by CBA of Giemsa-stained metaphases from bone marrow cells. A qualitative reverse transcriptase PCR on peripheral blood cells is mandatory to identify the type of BCR-ABL1 transcripts that can be appropriately followed when assessing response to TKI therapy. About 2–4% of patients harbor atypical BCR-ABL1 transcripts lacking ABL1 exon2 (e13a3 or e14a3) or resulting from atypical BCR breakpoints (e.g., e1a2, e6a2, e8a2, or e19a2) that may yield a false negative PCR using routine primer/probe sets in qualitative or quantitative reverse transcriptase PCR protocols. If not tested at diagnosis, a false impression may be given that a patient is in complete molecular response after TKI treatment. A quantitative PCR is not mandatory at diagnosis. If a molecular assay demonstrates BCR-ABL1, but the Ph-chromosome cannot be identified by cytogenetics, a FISH test is required.
- Of importance, more than 80% of recurrences occur within the first 6–8 months after stopping emphasizing the need for frequent monitoring and structured follow-up during this early period. Stopping treatment is a safe procedure at centers with access to high-quality molecular monitoring and with careful patient selection.
- Progression to advanced phase is rare (<2 per thousand patient-years with MMR). Continued molecular monitoring is nevertheless recommended indefinitely.”

### World Health Organization (WHO)

The WHO published guidelines on the 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).

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”).

## BCR-ABL 1 Testing AHS – M2027

“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.”

### College of American Pathologists (CAP) and American Society of Hematology (ASH)

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.

#### Statement

13: “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

#### Statement

14: “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.

### European Society for Medical Oncology (ESMO)

#### Chronic Myeloid Leukemia (CML)

The ESMO has published guidelines for diagnosis, treatment and follow-up of CML. These guidelines include a table which is shown below:

Table 2: Recommendations for diagnostic work-up, assessment of response and monitoring (Hochhaus et al., 2017)

Test	Baseline (diagnostic work-up)	To assess the response	To monitor the response and the treatment
Blood counts and differential	Yes	Every 15 days until a CHR [complete hematological response] without significant cytopenias has been achieved	Every 3 months

## BCR-ABL 1 Testing AHS – M2027

BM [bone marrow], cytology	Yes	No	No
BM, karyotype	Yes	At 3 and 6 months	Then every 6 months until CCyR [complete cytogenetic response] has been achieved
Blood, iFISH	No	No	Only if cytogenetics of BM metaphases cannot be analyzed or is normal and molecular response cannot be assessed
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 AP [accelerated phase] or BP [blast phase]	No	Only in the case of failure

The ESMO has also stated that a “diagnosis must be confirmed by cytogenetics showing t(9;22) (q34;q11), and by multiplex RT-PCR showing BCR-ABL1 transcripts” (Hochhaus et al., 2017). Other warning signs include “Major route cytogenetic aberrations (+8, iso(17q), +19, +22q-), chromosome 3 aberrations and BM fibrosis at diagnosis signs”; further, a quantification of BCR-ABL mRNA is required every 3 months (Hochhaus et al., 2017). Finally, the ESMO acknowledges that mutation analysis is “due” in case of failure of first-line therapy or if BCR-ABL transcript levels increase. However, ESMO recommends against baseline mutational analysis in patients with newly diagnosed CML-CP (Hochhaus et al., 2017).

### Acute Lymphoblastic Leukemia (ALL)

The ESMO also published clinical practice guidelines for ALL in 2016 and note that “standard cytogenetics/FISH and especially RT-PCR are routinely performed to obtain a rapid diagnosis of Ph+ ALL and identify certain intermediate/high- and high-risk karyotypes or gene, mainly:

- t(4;11)(q21;q23)/MLL-AFA4, abn11q23/MLL, t(1;19)(q23; p13)/PBX-E2A, t(8;14) or other abn14q32 in non-Burkitt ALL
  - del(6q), del(7p), del(17p), -7, +8, low hypodiploidy, i.e. with 30–39 chromosomes/near triploidy with 60–78 chromosomes
  - complex (≥5 unrelated clonal abnormalities), and
  - T-ALL lacking NOTCH1/FBXW7 mutations and/or with RAS/PTEN abnormalities
- The more prognostically favorable cytogenetic/genetic subsets are t(12;21)( p13;q22)/TEL-AML1 + ALL (rare in adults) and hyperdiploid ALL, and NOTCH-1/FBXW7-mutated T-ALL (Hoelzer et al., 2016).”

### **Applicable State and Federal Regulations**

#### **Food and Drug Administration (FDA)**

On September 27, 2019 the FDA approved Cepheid’s Xpert BCR-ABL Ultra, GeneXpert Dx System which is classified as a BCR-ABL1 monitoring test. The FDA states that this type of test is “a quantitative in vitro diagnostic device used to monitor the BCR/ABL1 to ABL1 ratio by reverse-transcriptase quantitative polymerase chain reaction (RQ-PCR) on whole blood or bone marrow of diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) patients expressing BCR-ABL1 fusion transcripts such as

## BCR-ABL 1 Testing AHS – M2027

e13a2 and/or e14a2. It is intended for use during monitoring of treatment response by reporting results on the international scale (%IS) and as log molecular reduction (MR) value (FDA, 2019a).”

On July 22, 2016 the FDA approved the QuantideX qPCR BCR-ABL IS Kit as an *in vitro* nucleic acid amplification test for the quantitation of BCR-ABL1 and ABL1 transcripts in total RNA from whole blood of diagnosed t(9;22) positive Chronic Myeloid Leukemia (CML) patients expressing BCR-ABL1 fusion transcripts type e13a2 and/or e14a2 as a class II device with special controls (FDA, 2016). Then, on February 13, 2019, the FDA approved the updated QXDx BCR-ABL %IS Kit from Biorad for use on the QXDx AutoDG ddPCR System to test RNA transcripts from whole blood (FDA, 2019b).

On December 22, 2017 the FDA approved the MolecularMD MRDx BCR-ABL Test as an *in vitro* diagnostic test for the quantitative detection of BCR-ABL1 transcripts (e13a2/b2a2 and/or e14a2/b3a2) and the ABL1 endogenous control mRNA in peripheral blood specimens from patients previously diagnosed with t(9;22) positive chronic myeloid leukemia (CML) as substantially equivalent (FDA, 2017).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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

---

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, 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**

---

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

Amin, H., & Ahmed, S. (2021). Molecular Monitoring of BCR-ABL Fusion Transcripts in Patients with Chronic Myeloid Leukemia During Treatment Using the Endpoint Fluorescence Method. *Laboratory Medicine*, 53(2), 183-189. doi:10.1093/labmed/lmab075

Ankathil, R., Azlan, H., Dzarr, A. A., & Baba, A. A. (2018). Pharmacogenetics and the treatment of chronic myeloid leukemia: how relevant clinically? An update. *Pharmacogenomics*. doi:10.2217/pgs-2017-0193

Arber, D. A., Borowitz, M. J., Cessna, M., Etzell, J., Foucar, K., Hasserjian, R. P., . . . Vardiman, J. W. (2017). Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med*, 141(10), 1342-1393. doi:10.5858/arpa.2016-0504-CP

Arber, D. A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M. J., Le Beau, M. M., . . . Vardiman, J. W. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, 127(20), 2391-2405. doi:10.1182/blood-2016-03-643544

## BCR-ABL 1 Testing AHS – M2027

Baccarani, M., Deininger, M. W., Rosti, G., Hochhaus, A., Soverini, S., Apperley, J. F., . . . Hehlmann, R. (2013). European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. doi:10.1182/blood-2013-05-501569

Bauer, S., & Romvari, E. (2012). Interpreting Molecular Monitoring Results and International Standardization in Chronic Myeloid Leukemia. *J Adv Pract Oncol*, 3(3), 151-160.

Brown, J. T., Beldorth, I. J., Laosinchai-Wolf, W., Fahey, M. E., Jefferson, K. L., Ruskin, A. K., . . . Andruss, B. F. (2019). Analytical Validation of a Highly Sensitive, Multiplexed Chronic Myeloid Leukemia Monitoring System Targeting BCR-ABL1 RNA. *The Journal of molecular diagnostics : JMD*, 21(4), 718-733. doi:10.1016/j.jmoldx.2019.03.002

D'Adda, M., Farina, M., Schieppati, F., Borlenghi, E., Bottelli, C., Cerqui, E., . . . Rossi, G. (2019). The e13a2 BCR-ABL transcript negatively affects sustained deep molecular response and the achievement of treatment-free remission in patients with chronic myeloid leukemia who receive tyrosine kinase inhibitors. *Cancer*, 0(0). doi:10.1002/cncr.31977

Dulucq, S., Etienne, G., Morisset, S., Klein, E., Chollet, C., Robbesyn, F., . . . Mahon, F. X. (2019). Impact of second decline rate of BCR-ABL1 transcript on clinical outcome of chronic phase chronic myeloid leukemia patients on imatinib first-line. *Ann Hematol*, 98(5), 1159-1168. doi:10.1007/s00277-019-03633-x

FDA. (2016). *EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR QUANTIDEX QPCR BCR-ABL IS KIT DECISION SUMMARY*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/DEN160003.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160003.pdf).

FDA. (2017). *MolecularMD MRDx® BCR-ABL Test 510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY*. U.S. Food and Drug Administration Retrieved from [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/K173492.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/K173492.pdf).

FDA. (2019a). Product Classification. Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/classification.cfm?id=4999>

FDA. (2019b, February 13). QXDx BCR-ABL %IS Kit for use on the QXDx AutoDG ddPCR System. Retrieved from [https://www.accessdata.fda.gov/cdrh\\_docs/pdf18/K181661.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181661.pdf)

Goldberg, S. L., Chen, L., Guerin, A., Macalalad, A. R., Liu, N., Kaminsky, M., . . . Wu, E. Q. (2013). Association between molecular monitoring and long-term outcomes in chronic myelogenous leukemia patients treated with first line imatinib. *Curr Med Res Opin*, 29(9), 1075-1082. doi:10.1185/03007995.2013.812034

Greenfield, G., McMullan, R., Robson, N., McGimpsey, J., Catherwood, M., & McMullin, M. F. (2019). Response to Imatinib therapy is inferior for e13a2 BCR-ABL1 transcript type in comparison to e14a2 transcript type in chronic myeloid leukaemia. *BMC Hematol*, 19, 7. doi:10.1186/s12878-019-0139-2

Guerin, A., Chen, L., Dea, K., Wu, E. Q., & Goldberg, S. L. (2014a). Association between regular molecular monitoring and tyrosine kinase inhibitor therapy adherence in chronic myelogenous leukemia in the chronic phase. *Curr Med Res Opin*, 30(7), 1345-1352. doi:10.1185/03007995.2014.904281

Guerin, A., Chen, L., Dea, K., Wu, E. Q., & Goldberg, S. L. (2014b). Economic benefits of adequate molecular monitoring in patients with chronic myelogenous leukemia. *J Med Econ*, 17(2), 89-98. doi:10.3111/13696998.2013.862251

## BCR-ABL 1 Testing AHS – M2027

- Hochhaus, A., Lin, F., Reiter, A., Skladny, H., Mason, P., Rhee, F. v., . . . Cross, N. (1996). Quantification of residual disease in chronic myelogenous leukemia patients on interferon-alpha therapy by competitive polymerase chain reaction. *Blood*.
- Hochhaus, A., Saussele, S., Rosti, G., Mahon, F. X., Janssen, J., Hjorth-Hansen, H., . . . Buske, C. (2017). Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 28(suppl\_4), iv41-iv51. doi:10.1093/annonc/mdx219
- Hoelzer, D., Bassan, R., Dombret, H., Fielding, J., Ribera, M., & Buske, C. (2016). ESMO Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer. Retrieved from <https://www.esmo.org/guidelines/haematological-malignancies/acute-lymphoblastic-leukaemia>
- Hughes, T., Deininger, M., Hochhaus, A., Branford, S., Radich, J., Kaeda, J., . . . Goldman, J. M. (2006). Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*, 108(1), 28-37. doi:10.1182/blood-2006-01-0092
- Kantarjian, H. M., Talpaz, M., Cortes, J., O'Brien, S., Faderl, S., Thomas, D., . . . Arlinghaus, R. (2003). Quantitative polymerase chain reaction monitoring of BCR-ABL during therapy with imatinib mesylate (STI571; gleevec) in chronic-phase chronic myelogenous leukemia. *Clin Cancer Res*, 9(1), 160-166.
- Kurzrock, R., Kantarjian, H. M., Druker, B. J., & Talpaz, M. (2003). Philadelphia chromosome-positive leukemias: from basic mechanisms to molecular therapeutics. *Ann Intern Med*, 138(10), 819-830.
- Latremouille-Viau, D., Guerin, A., Gagnon-Sanschagrin, P., Dea, K., Cohen, B. G., & Joseph, G. J. (2017). Health Care Resource Utilization and Costs in Patients with Chronic Myeloid Leukemia with Better Adherence to Tyrosine Kinase Inhibitors and Increased Molecular Monitoring Frequency. *J Manag Care Spec Pharm*, 23(2), 214-224. doi:10.18553/jmcp.2017.23.2.214
- Leoni, V., & Biondi, A. (2015). Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia. *Haematologica*, 100(3), 295-299. doi:10.3324/haematol.2015.124016
- Li, S., Ilaria, R. L., Jr., Million, R. P., Daley, G. Q., & Van Etten, R. A. (1999). The P190, P210, and P230 forms of the BCR/ABL oncogene induce a similar chronic myeloid leukemia-like syndrome in mice but have different lymphoid leukemogenic activity. *J Exp Med*, 189(9), 1399-1412.
- Lima, L., Bernal-Mizrachi, L., Saxe, D., Mann, K. P., Tighiouart, M., Arellano, M., . . . Khoury, H. J. (2011). Peripheral blood monitoring of chronic myeloid leukemia during treatment with imatinib, second-line agents, and beyond. *Cancer*, 117(6), 1245-1252. doi:10.1002/cncr.25678
- Mahon, F. X., Rea, D., Guilhot, J., Guilhot, F., Huguet, F., Nicolini, F., . . . Rousselot, P. (2010). Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*, 11(11), 1029-1035. doi:10.1016/s1470-2045(10)70233-3
- Milojkovic, D., & Apperley, J. (2009). Mechanisms of Resistance to Imatinib and Second-Generation Tyrosine Inhibitors in Chronic Myeloid Leukemia. *Clin Cancer Res*, 15(24), 7519-7527. doi:10.1158/1078-0432.ccr-09-1068
- NCCN. (2021, October 22). NCCN Clinical Practice Guidelines in Oncology Pediatric Acute Lymphoblastic Leukemia Version 1.2022. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/ped\\_all.pdf](https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf)
- NCCN. (2022a, April 6). NCCN Clinical Practice Guidelines in Oncology Acute Lymphoblastic Leukemia Version 1.2022. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/all.pdf](https://www.nccn.org/professionals/physician_gls/pdf/all.pdf)

## BCR-ABL 1 Testing AHS – M2027

- NCCN. (2022b, January 13). NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia Version 3.2022. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/cml.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf)
- Negrin, R., & Schiffer, C. (2018). Overview of the treatment of chronic myeloid leukemia - UpToDate. In A. Rosmarin (Ed.), UpToDate. Retrieved from [https://www.uptodate.com/contents/overview-of-the-treatment-of-chronic-myeloid-leukemia?topicRef=4543&source=see\\_link#H11](https://www.uptodate.com/contents/overview-of-the-treatment-of-chronic-myeloid-leukemia?topicRef=4543&source=see_link#H11).
- Nowell, P., & Hungerford, D. (1960). A minute chromosome in human granulocytic leukemia. *Science*, 1497. doi:10.1126/science.132.3438.1488
- O'Hare, T., Eide, C. A., & Deininger, M. W. (2007). Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. *Blood*, 110(7), 2242-2249. doi:10.1182/blood-2007-03-066936
- Pagani, I. S., Dang, P., Saunders, V. A., Braley, J., Thieleke, A., Branford, S., . . . Ross, D. M. (2020). Clinical utility of genomic DNA Q-PCR for the monitoring of a patient with atypical e19a2 BCR-ABL1 transcripts in chronic myeloid leukemia. *Leuk Lymphoma*, 61(10), 2527-2529. doi:10.1080/10428194.2020.1772476
- PDQ. (2019). Adult Acute Lymphoblastic Leukemia Treatment (PDQ®). Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK65727/>
- Pui, C. H. (2011). Recent advances in acute lymphoblastic leukemia. *Oncology (Williston Park)*, 25(4), 341, 346-347.
- Ren, R. (2005). Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. *Nat Rev Cancer*, 5(3), 172-183. doi:10.1038/nrc1567
- Ross, D. M., Branford, S., Seymour, J. F., Schwarzer, A. P., Arthur, C., Yeung, D. T., . . . Hughes, T. P. (2013). Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*, 122(4), 515-522. doi:10.1182/blood-2013-02-483750
- Schiffer, C. A., & Atallah, E. (2020, April 27). Overview of the treatment of chronic myeloid leukemia. *UpToDate*. Retrieved from <https://www.uptodate.com/contents/overview-of-the-treatment-of-chronic-myeloid-leukemia>
- Schrijver, I., Zehnder, J., & Cherry, A. (2018). Genetic abnormalities in hematologic and lymphoid malignancies - UpToDate. In A. Rosmarin (Ed.), UpToDate. Retrieved from [https://www.uptodate.com/contents/genetic-abnormalities-in-hematologic-and-lymphoid-malignancies?search=bcr%20abl%20fusion%20gene&source=search\\_result&selectedTitle=6~36&usage\\_type=default&display\\_rank=6#H69719826](https://www.uptodate.com/contents/genetic-abnormalities-in-hematologic-and-lymphoid-malignancies?search=bcr%20abl%20fusion%20gene&source=search_result&selectedTitle=6~36&usage_type=default&display_rank=6#H69719826).
- Smith, A. G., Russell, J., Feldman, E. L., Goldstein, J., Peltier, A., Smith, S., . . . Singleton, J. R. (2006). Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care*, 29(6), 1294-1299. doi:10.2337/dc06-0224
- Soverini, S., Hochhaus, A., Nicolini, F. E., Gruber, F., Lange, T., Saglio, G., . . . Martinelli, G. (2011). 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*, 118(5), 1208-1215. doi:10.1182/blood-2010-12-326405
- Tachibana, T., Kondo, T., Uchida, N., Doki, N., Takada, S., Takahashi, S., . . . on behalf of the adult, C. w. g. o. t. J. S. f. T. a. C. T. (2022). The clinical significance of BCR-ABL1 mutations in patients with Philadelphia chromosome-positive chronic myeloid leukemia who underwent allogeneic hematopoietic cell transplantation. *Transplantation and Cellular Therapy*. doi:<https://doi.org/10.1016/j.jctc.2022.03.00>



## BCR-ABL 1 Testing AHS – M2027

Van Etten, R. (2020, July 29). Clinical manifestations and diagnosis of chronic myeloid leukemia - UpToDate. UpToDate. Retrieved from <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-myeloid-leukemia>

Van Etten, R. (2021, May 21). Cellular and molecular biology of chronic myeloid leukemia - UpToDate. UpToDate. Retrieved from [https://www.uptodate.com/contents/cellular-and-molecular-biology-of-chronic-myeloid-leukemia?sectionName=c-ABL1&topicRef=4537&anchor=H11&source=see\\_link#H11](https://www.uptodate.com/contents/cellular-and-molecular-biology-of-chronic-myeloid-leukemia?sectionName=c-ABL1&topicRef=4537&anchor=H11&source=see_link#H11).

Verma, D., Kantarjian, H. M., Jones, D., Luthra, R., Borthakur, G., Verstovsek, S., . . . Cortes, J. (2009). Chronic myeloid leukemia (CML) with P190 BCR-ABL: analysis of characteristics, outcomes, and prognostic significance. *Blood*, *114*(11), 2232-2235. doi:10.1182/blood-2009-02-204693

Warmuth, M., Danhauser-Riedl, S., & Hallek, M. (1999). Molecular pathogenesis of chronic myeloid leukemia: implications for new therapeutic strategies. *Ann Hematol*, *78*(2), 49-64.

Yeung, C. C., Egan, D., & Radich, J. P. (2016). Molecular monitoring of chronic myeloid leukemia: present and future. *Expert Rev Mol Diagn*, *16*(10), 1083-1091. doi:10.1080/14737159.2016.1227243

Yu, S., Cui, M., He, X., Jing, R., & Wang, H. (2017). A review of the challenge in measuring and standardizing BCR-ABL1. *Clin Chem Lab Med*, *55*(10), 1465-1473. doi:10.1515/cclm-2016-092

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

Specialty Matched Consultant Advisory Panel 8/2021

Medical Director review 8/2022

## **Policy Implementation/Update Information**

---

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

- 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)

## BCR-ABL 1 Testing AHS – M2027

### 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)
- 9/7/21 Reviewed by Avalon Q2 2021 CAB. Reviewed by Medical Director 7/2021. Updated Description, Policy Guidelines, and References. Under “When Covered” section statement #4 a. edited “There is failure to reach response milestones.” Statement #4 b. edited “There is any sign of loss of response (defined as hematologic or cytogenetic relapse).” Specialty Matched Consultant Advisory Panel review 8/18/2021. (lpr)
- 9/13/22 Reviewed by Avalon 2<sup>nd</sup> Quarter 2022 CAB. Medical Director review 8/2022. Clarified When Covered section. Updated policy guidelines and references. Under Billing/Coding section, removed CPT code 81401. (lpr)

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.