BCR-ABL 1 Testing for Chronic Myeloid Leukemia

Policy Number: **AHS – M2027 – BCR-ABL 1 Testing for Chronic Myeloid Leukemia**

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**Policy Description**

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, 2018a). 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 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**

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**Indications and/or Limitations of Coverage**

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.
1. Qualitative or quantitative RT-PCR testing for identification of the BCR-ABL1 fusion gene transcript type **MEETS COVERAGE CRITERIA** for the differential diagnosis of CML or ALL.

2. 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 prior to initiation or undergoing treatment with TKI therapy, **MEETS COVERAGE CRITERIA**:  
   a. As a baseline measurement prior to initiation of TKI therapy  
   b. Every 3 months after initiation of therapy after MMR (BCR-ABL1 (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-ABL1 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, **MEETS COVERAGE CRITERIA**.

4. Evaluation of BCR-ABL kinase domain point mutations in patients with CML **MEETS COVERAGE CRITERIA** 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-ABL1 transcript levels and loss of MMR, OR  
   d. 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-ALL, using the International Scale reporting convention, **MEETS COVERAGE CRITERIA** for optimal risk stratification, treatment planning, surveillance, and MRD assessment.

6. Evaluation of BCR-ABL kinase domain point mutations in patients with ALL **MEETS COVERAGE CRITERIA** when there is relapsed or refractory disease in Ph positive ALL patients.

7. Testing of both bone marrow and blood for monitoring purposes **DOES NOT MEET COVERAGE CRITERIA**.

**Scientific Background**

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 to form the transcriptionally active BCR/ABL fusion gene (Schrijver et al., 2018). 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) that
activates a number of downstream signaling molecules, including PI3K, AKT, JNK, RAS and STAT5 (Ren, 2005), disrupting cellular signal transduction pathways, and regulation of both apoptosis and cell proliferation (Warmuth, Danhauser-Riedl, & Hallek, 1999), ultimately leading to factor-independent and leukemogenic cell growth (Van Etten, 2018a).

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 et al., 2018). Independent of which other chromosomes are involved in variant translocations, the generation of the BCR/ABL fusion gene is the “fundamental cause of Ph-positive leukemias” (Van Etten, 2018a), 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, which eventually led to the creation of tyrosine kinase inhibitors (TKIs) (Negrin & Schiffer, 2018a). Protein kinases had been thought to be poor therapeutic targets because of their ubiquitous nature and crucial role in many normal physiologic processes. 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, competitively inhibiting the adenosine triphosphate-binding site of the BCR/ABL oncoprotein (Negrin & Schiffer, 2018a). 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, 2018a). 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 being produced to inhibit additional signaling pathways or overcome resistance (Negrin & Schiffer, 2018a).

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, 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, 2018a). 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, 2018a; 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, 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-ABL1 fusion gene or the BCR-ABL1 fusion mRNA, by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR) (Van Etten, 2018b). 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.
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 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 BCR-ABL1 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 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, quantities 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 (Negrin & Schiffer, 2018b).

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).

Clinical Validity and Utility

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”. 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).”. They concluded that “This correlation was not affected by the presence of the Ph+ 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 of 180 patients with Philadelphia chromosome (Ph)-positive chronic-phase, treated with imatinib mesylate by quantitative competitive PCR (QC-PCR). They found 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%).” They concluded that “QC-PCR studies provide a useful tool to monitor patients with CML on imatinib mesylate therapy (Kantarjian et al., 2003).”

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).
Goldberg et al. (2013) performed a retrospective chart review of 402 CML-CP patients on first-line imatinib therapy analyzing the impact of molecular monitoring frequency on the risk of progression and progression-free survival. They 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 (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).”

Guérin et al. (2014a) performed a retrospective cohort study of 1205 diagnosed chronic phase CML patients obtained from two large US administrative claims databases. 41% of these 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).

Guérin et al. (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. 41% 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).”

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. They 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).

D’Adda et al. evaluated the effect of the BCR-ABL transcript on efficacy of TKIs. 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).

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 have 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; however recently, next-generation sequencing (NGS) is being utilized as a more sensitive and effective method, able to detect lower frequency and earlier existence of mutations, to enable more effective therapeutic tailoring (Ankathil et al., 2018). BCR/ABL
mutation screening is clinically relevant to identify CML patients who are likely to have poor outcome as mutations in different regions of BCR/ABL tyrosine kinase domain lead to different levels of resistance (Smith et al., 2006) and the type of mutation can 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 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).

Guidelines and Recommendations

The National Comprehensive Cancer Network (NCCN, 2019b) recommendations for CML indicate:

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Bone marrow cytogenetics&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach response milestones</td>
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<tr>
<td></td>
<td>• Any signs of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td>qPCR using IS</td>
<td>• At diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Every 3 months after initiating treatment. After BCR-ABL&lt;sub&gt;1&lt;/sub&gt; (IS) ≤1% (&gt;0.1% - 1%) has been achieved, every 3 months for 2 years and every 3 – 6 months thereafter</td>
</tr>
<tr>
<td></td>
<td>• If there is 1-log increase in BCR-ABL&lt;sub&gt;1&lt;/sub&gt; transcript levels with MMR, qPCR should be repeated in 1 – 3 months</td>
</tr>
<tr>
<td>BCR-ABL kinase domain mutation analysis</td>
<td>• Chronic phase</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach response milestones</td>
</tr>
<tr>
<td></td>
<td>• Any sign of loss of response (defined as hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td></td>
<td>• 1-log increase in BCR-ABL&lt;sub&gt;1&lt;/sub&gt; transcript levels and loss of MMR</td>
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<tr>
<td></td>
<td>• Disease progression to accelerated or blast phase</td>
</tr>
</tbody>
</table>

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

The National Comprehensive Cancer Network (NCCN, 2019a) guidelines for ALL indicate:

The NCCN recommends testing of marrow or peripheral blood lymphoblasts using various genetic techniques, such as:

- Karyotyping of G-banded metaphase chromosomes
- 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).

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)).

- Additional assessment (array cGH) in cases of aneuploidy or failed karyotype
- BCR-ABL kinase domain mutation analysis for relapsed/refractory disease

In 2019, the NCCN issued a new set of guidelines titled *Pediatric Acute Lymphoblastic Leukemia*. For pediatric acute lymphoblastic leukemia (PEDALL), they recommend testing for gene fusions and mutations associated with Ph-like ALL if a pediatric individual has tested BCR-ABL1 negative. They also state, “consider periodic BCR-ABL1 transcript-specific quantification (Ph+ ALL)”. The NCCN table of potentially actionable or prognostic mutations for PEDALL is given below (NCCN, 2019c):

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable risk features</td>
<td>High hyperdiploidy (51 – 67 chromosomes)&lt;br&gt;  • Trisomy of chromosomes 4, 10, and 17 have the most favorable outcome</td>
</tr>
<tr>
<td></td>
<td>Cryptic t(12;21)(p13;q22):&lt;br&gt;  • ETV6-RUNX1 fusion</td>
</tr>
<tr>
<td>Unfavorable risk features</td>
<td>Hypodiploidy (&lt;44 chromosomes)</td>
</tr>
<tr>
<td></td>
<td>KMT2Ar (t[4;11] or others)</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34;q11.2)</td>
</tr>
<tr>
<td></td>
<td>• BCR-ABL1</td>
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<tr>
<td></td>
<td><strong>BCR-ABL1-like (Ph-like) ALL</strong></td>
</tr>
<tr>
<td></td>
<td>• JAK-STAT</td>
</tr>
<tr>
<td></td>
<td>o CRLF2r</td>
</tr>
<tr>
<td></td>
<td>o EPORr</td>
</tr>
<tr>
<td></td>
<td>o JAK1/2/3r</td>
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<tr>
<td></td>
<td>o TYK2r</td>
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<tr>
<td></td>
<td>o SH2B3 mutations</td>
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<tr>
<td></td>
<td>o IL7R mutations</td>
</tr>
<tr>
<td></td>
<td>o JAK1/2/3 mutations</td>
</tr>
<tr>
<td></td>
<td>• ABL class rearrangements of:&lt;br&gt;  o ABL1&lt;br&gt;  o ABL2&lt;br&gt;  o PDGFRA&lt;br&gt;  o PDGFRB&lt;br&gt;  o FGFR</td>
</tr>
<tr>
<td></td>
<td>• Other&lt;br&gt;  o NTRKo&lt;br&gt;  o FLT3aro&lt;br&gt;  o LYNr&lt;br&gt;  o PTL2Bro</td>
</tr>
<tr>
<td></td>
<td>t(17;19)</td>
</tr>
<tr>
<td></td>
<td>• TCF3-HLF fusion</td>
</tr>
<tr>
<td></td>
<td>Intrachromosomal amplification of chromosome 21 (iAMP21)</td>
</tr>
<tr>
<td></td>
<td>Alterations of IZKF1†</td>
</tr>
</tbody>
</table>

† NOTE: The NCCN states, “Emerging evidence suggests DUX4r ALL is favorable. Additionally in cases of DUX4r, IZKF1 alterations do not confer poor prognosis (NCCN, 2019c).”
Guidelines from the European Society for Medical Oncology (Hochhaus et al., 2017):

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

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 major molecular response (MMR, MR3.0 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 $10^{-4}$, 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 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.”

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

In the recent revision of the 4th 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+, 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.

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

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)**

ESMO notes that standard cytogenetics/FISH and RT-PCR are routinely performed to identify certain intermediate or high-risk karyotypes or gene rearrangements in ALL. These include:

- 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 (ESMO, 2016)

ESMO also released guidelines discussing BCR-ABL’s role in CML. They stated that diagnosis of CML must be confirmed by "cytogenetics showing t(9;22)(q34;q11), and by multiplex RT-PCR
showing BCR-ABL1 transcripts”. Other warning signs included “Major route cytogenetic aberrations (+8, iso(17q), +19, +22q-), chromosome 3 aberrations and BM fibrosis at diagnosis signs”. A quantification of BCR-ABL mRNA is required every 3 months. ESMO also 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 (ESMO et al., 2017).

State and Federal Regulations, as applicable

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. 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.

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.

### Applicable CPT/HCPCS Procedure Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81170</td>
<td>ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain</td>
</tr>
<tr>
<td>81206</td>
<td>BCR/ABL1 (t(9:22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative</td>
</tr>
<tr>
<td>81207</td>
<td>Minor breakpoint, qualitative or quantitative</td>
</tr>
<tr>
<td>81208</td>
<td>Other breakpoint, qualitative or quantitative</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) –GENES: ABL (c-abl oncogene 1, receptor tyrosine kinase) (e.g., acquired imatinib resistance), T315I variant</td>
</tr>
<tr>
<td>0016U</td>
<td>Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation Proprietary test: QuantideX® qPCR BCR-ABL Test Lab/Manufacturer: University of Iowa, Department of Pathology, Asuragen</td>
</tr>
<tr>
<td>0040U</td>
<td>BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative Proprietary test: MRDx® BCR-ABL Test Lab/Manufacturer: MolecularMD</td>
</tr>
</tbody>
</table>


Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.
Evidence-based Scientific References


doi:10.3111/13696998.2013.862251


**Policy Implementation/Update Information**

1/1/20 New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.