CLINICAL MEDICAL POLICY

<table>
<thead>
<tr>
<th>Policy Name:</th>
<th>BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia</th>
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<tbody>
<tr>
<td>Policy Number:</td>
<td>MP-017-MD-DE</td>
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<tr>
<td>Approved By:</td>
<td>Medical Management</td>
</tr>
<tr>
<td>Provider Notice Date:</td>
<td>11/1/2016</td>
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<tr>
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<tr>
<td>Products:</td>
<td>Highmark Health Options</td>
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<tr>
<td>Application:</td>
<td>All participating hospitals and providers</td>
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<tr>
<td>Page Number(s):</td>
<td>1 of 9</td>
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Disclaimer

Highmark Health Options medical payment and prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options provides coverage under the medical laboratory testing benefits of the Company's Medicaid products for medically necessary Philadelphia chromosome (BCR-ABL1) testing.

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances warrants individual consideration, based on review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.
DEFINITIONS

Philadelphia Chromosome – A cytogenetic abnormality of chromosome 22 where part of chromosome 9 is transferred to it, called translocation. The new chromosome which is now mostly chromosome 22 with a piece of chromosome 9 attached to it is called the Philadelphia chromosome. Bone marrow cells that contain the Philadelphia chromosome are commonly found in acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML) and chronic myelogenous leukemia. The chromosome abnormality is identified either by cytogenetics or molecular testing. Specimens for testing include bone marrow or peripheral whole blood.

Tyrosine Kinase – Any of a family of enzymes that phosphorylate tyrosine in certain proteins and play an important role in cell signaling. Mutations that affect their activity or expression are found in human diseases, including chronic myeloid (myelogenous) leukemia.

Acute Lymphoblastic Leukemia (ALL) – Is a disease characterized by the proliferation if immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is most common of childhood tumors and represents 75 to 80% of acute leukemias in children. ALL affects only 20% of all leukemias in adults.

Chronic Myelogenous Leukemia (CML) – Is a disease of a malignant disorder of myeloid hematopoietic stem cells which accounts for approximately 15% of adult leukemias. The disease progresses in three phase: chronic, accelerated and blast phases and most people are diagnosed during the chronic phase. The presence of the Philadelphia chromosome and/or confirmation of the BCR-ABL1 fusion gene is essential to the diagnosis of CML.

BCR/ABL1 – A fusion gene that is found in several types of cancer and it formed by an exchange genetic material between the ABL gene on chromosome 9 and the BCR gene on chromosome 22, forming the BCR/ABL fusion gene. This altered chromosome 22 with the BCR/ABL fusion gene is called the Philadelphia chromosome. Types of BCR/ABL testing include:
  • BCR/ABL Fish cytogenetic testing – indicated in order to detect the BCR/ABL fusion gene and provide an estimate of the percentage of cells carrying the fusion gene
  • Quantitative - indicated for monitoring of disease for any patient positive for the BCR/ABL fusion gene by qualitative assay
  • Qualitative – indicated in the initial evaluation for patients known to have a positive FISH cytogenetic test for BCR/ABL

PROCEDURES

1) The following medical necessity criteria must be met:

   Chronic myeloid leukemia (CML)
     a) BCR/ABL1 qualitative testing (blood or bone marrow) is medically necessary for the diagnosis of CML since this information is necessary for subsequent quantitative testing of fusion gene messenger RNA transcripts
b) BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (blood or bone marrow) is necessary for monitoring CML treatment response and remission:
   1. Baseline prior to initiation of treatment; AND
   2. At appropriate intervals during therapy:
      • Every three months after the start of treatment, including three months, six months follow-up
      • Without achieving complete response, continued monitoring at three month intervals is recommended
      • After complete cytogenetic response is reached, every three months for 2 years, then every three to six months

c) ABL kinase domain point mutations (blood or bone marrow) are necessary to evaluate patients for tyrosine kinase inhibitor resistance when:
   1. There is inadequate initial response to treatment at three, six and 12 months; OR
   2. Any sign of loss or response; OR
   3. There is progression of the disease to accelerate or blast phase

Acute Lymphoblastic Leukemia (ALL)
   a) Determining the qualitative presence of the BCR-ABL1 fusion gene is necessary to establish a diagnosis of ALL
   b) BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain is necessary for monitoring Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission when:
      1. At baseline prior to initiation of treatment; and
      2. At appropriate intervals during therapy
      3. Optimal timing of monitoring remains unclear
   c) ABL kinase domain point mutations for monitoring are medically necessary to evaluate patients for tyrosine kinase inhibitor resistance when:
      1. There is inadequate initial response to treatment at three, six and 12 months; OR
      2. At any time with there are any signs of loss of response.

2) When BCR/ALB mutation analysis service are not covered
   For all other conditions other than those listed above scientific evidence has not been established and therefore not medically necessary in the management of CML and ALL.

3) Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

4) Place of Service
   The place of service for the Philadelphia Chromosome testing is typically as an outpatient.
5) Genetic Counseling
Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician with experience in cancer genetics
- A physician specializing in the care required for this patient’s condition

6) Governing Bodies Approval
FDA
  a) The BCR/ALB genetic tests are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

CODING REQUIREMENTS

**Procedure Codes**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81170</td>
<td>ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain</td>
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<tr>
<td>81206</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative</td>
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<tr>
<td>81207</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative</td>
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<tr>
<td>81208</td>
<td>BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative</td>
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<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)</td>
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</table>
Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in two or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) (e.g., ABL1 kinase domain)

<table>
<thead>
<tr>
<th>Diagnosis Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>C91.0</td>
<td>Acute lymphoblastic leukemia (ALL)</td>
</tr>
<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia, not having achieved remission</td>
</tr>
<tr>
<td>C91.01</td>
<td>Acute lymphoblastic leukemia, in remission</td>
</tr>
<tr>
<td>C91.02</td>
<td>Acute lymphoblastic leukemia, in relapse</td>
</tr>
<tr>
<td>C92.10</td>
<td>Chronic myeloid leukemia, BCR/ABL positive, not having achieved remission</td>
</tr>
<tr>
<td>C92.11</td>
<td>Chronic myeloid leukemia, BCR/ABL positive, in remission</td>
</tr>
<tr>
<td>C92.12</td>
<td>Chronic myeloid leukemia, BCR/ABL positive, in relapse</td>
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**REIMBURSEMENT**

Participating facilities will be reimbursed per their Highmark Health Options contract.

**POLICY SOURCE(S)**


### Monitoring Schedule

<table>
<thead>
<tr>
<th>Response Level</th>
<th>Definition</th>
<th>Monitoring Frequency/Schedule</th>
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<tr>
<td>Hematologic Complete Hematologic Response (CHR)</td>
<td>A hematologic response (HR) is one that happens with blood counts. For example, when diagnosed your white count may have been quite high. A positive hematologic response would be indicated by a decrease in your white count. For practical purposes, a HR means that your blood counts have returned to the normal range. When the counts return to the normal range, it is said that you have had a COMPLETE hematological response (CHR).</td>
<td>Blood test at diagnosis and then every 15 days until CHR has been achieved and confirmed. Then at least every 3 months or as required.</td>
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</table>
| Cytogenetic | A **cytogenetic response** is indicated by the number (or percentage) of Philadelphia Chromosome positive (PH+) cells contained in the bone marrow. A complete cytogenetic response (CCyR) indicates that no PH+ metaphases are present in the sample. PCyR indicates that only 1 - 35% of the sample contains PH+ metaphases. Minimal: 35 - 65%. Minor: 66 - 95%.
| Complete (CCyR) | During this cytogenetic test, the Cytotechnologist literally counts cells in a sample. They look at 100 cells and base the percentages on that sample. Thus, one would have achieved CCyR when no CML cells are found in the sample. PCyR when 1 - 34 cells were found, etc.
| Partial (PCyR) | The results from this test do not suggest that there are no CML remaining - rather, it indicates the level at which the bone marrow has been cleared of CML cells. Once on has achieved CCyR, a more sensitive molecular test (RT-Q-PCR - Realtime Quantitative Polymerase Chain Reaction).
| Minor | **At diagnosis, 3 months, and 6 months**, then **every 6 months** until CCyR has been achieved and confirmed.
| Minimal | After 12 months, if an MMR is achieved in molecular studies, cytogenetic testing on bone marrow is required only if standardized molecular testing is not available.

| Molecular | **A molecular response** is determined using the highest level of monitoring available for the CML patient. A **complete molecular response** indicates the BCR-ABL gene (a.k.a. the Philadelphia Chromosome) is undetectable in 2 consecutive blood samples as tested via Real Time Quantitative and/or nested Polymerase Chain Reaction (PCR).
| Complete Molecular Response (CMR) | As PCR testing has become more sensitive, one may see response levels of MR4.0, MR 4.5, and MR5.0 instead of "CMR." These newer designations indicate molecular responses at 4, 4.5, and 5 logs.
| Major Molecular Response (MMR) | A **major molecular response** indicates that the ratio of BCR-ABL to ABL (CML cells to normal [those not containing the Philadelphia chromosome] cells) is less than, or equal to 0.1 on the International Scale (IS). MMR is a three (3) log reduction of one's CML from baseline levels shown at diagnosis.
| | **RT-Q-PCR:** Every 3 months until MMR has been achieved and confirmed, then at least **every 6 months**.
| Mutational analysis: In occurrences of suboptimal response or failure, should **ALWAYS** be required before changing to another TKI or therapy.

From: National CML Society adapted from the 2014 NCCN and European Leukemia Guidelines for CML.
## Timing of Cytogenetic and Molecular Monitoring

<table>
<thead>
<tr>
<th>Condition</th>
<th>Monitoring Methodology</th>
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<tbody>
<tr>
<td>At diagnosis</td>
<td>CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type).</td>
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<tr>
<td>During treatment</td>
<td>RQ-PCR every 3 months until MMR has been achieved, then every 3 to 6 months and/or CBA at 3, 6, and 12 months until CCyR has been achieved, then every 12 months. Once CCyR is achieved, FISH on blood cells can be used.</td>
</tr>
<tr>
<td>Failure, progression</td>
<td>RQ-PCR, mutational analysis, and CBA. Immunophenotyping in blast phase.</td>
</tr>
<tr>
<td>Warning</td>
<td>Molecular and cytogenetic tests more frequently. CBA in case of myelodysplasia or CCA/Ph-.</td>
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CBA: Chromosome banding analysis of marrow cell metaphases at least 20 metaphases analysed.


## Example BCR/ABL Testing Flow Chart

![Example BCR/ABL Testing Flow Chart](image-url)