



CLINICAL MEDICAL POLICY	
<b>Policy Name:</b>	BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
<b>Policy Number:</b>	MP-017-MD-PA
<b>Responsible Department(s):</b>	Medical Management
<b>Provider Notice/Issue Date:</b>	02/01/2025; 03/01/2024; 02/01/2023; 04/01/2022; 2/13/2021; 02/17/2020; 03/18/2019; 04/15/2018; 10/01/2016
<b>Effective Date:</b>	03/01/2025; 04/01/2024; 03/01/2023; 05/01/2022; 3/15/2021; 03/16/2020; 03/18/2019; 04/15/2018; 10/01/2016
<b>Next Annual Review:</b>	11/2025
<b>Revision Date:</b>	11/20/2024; 11/15/2023; 11/17/2021; 11/18/2020; 11/20/2019; 11/14/2018; 12/12/2017; 08/09/2017; 3/15/2017
<b>Products:</b>	Highmark Wholecare <sup>SM</sup> Medicaid
<b>Application:</b>	All participating hospitals and providers
<b>Page Number(s):</b>	1 of 12

#### Policy History

Date	Action
03/01/2025	Provider Effective date
01/13/2025	PARP Approval
11/20/2024	QI/UM Committee review
11/20/2024	Annual Review: No changes to clinical criteria. Updated 'Reference Sources' section.
04/01/2024	Provider Effective date
01/24/2024	PARP Approval
11/15/2023	QI/UM Committee review
11/15/2023	Annual Review: No changes to clinical criteria. Reformatted 'Procedures' section. Updated 'Summary of Literature' and 'Reference Sources' sections. Updated the code description of the following ICD-10 codes: C92.10, C92.11, C92.12, C92.90, C92.91, & C92.92.
03/01/2023	Provider Effective date
01/10/2023	PARP Approval
11/16/2022	QI/UM Committee review
11/16/2022	Annual Review: No changes to clinical criteria. Reformatted 'Procedures' section numbering. Updated 'Summary of Literature' and 'Reference Sources' sections.

05/01/2022	Provider Effective date
03/09/2022	PARP Approval
11/17/2021	QI/UM Committee review
11/17/2021	Annual Review: No changes to clinical criteria. Revised wording of Procedures section. Added TAG determination information. Updated Summary of Literature and Reference sections. Updated coding description for diagnosis code C92.92, per AMA guidance.
03/15/2021	Provider effective date
02/02/2021	PARP approval
11/18/2020	QI/UM Committee review
11/18/2020	Annual Review: Updated criteria for frequency of BCR-ABL1 testing in CML. Removed hyperlinks. Updated Summary of Literature and References section with most recent NCCN guidelines.
03/16/2020	Provider effective date
01/16/2020	PARP Approval
11/20/2019	QI/UM Committee Review
11/20/2019	Annual Review: No criteria changes
03/18/2019	Provider Effective Date
05/05/2016	Initial policy developed

### **Disclaimer**

Highmark Wholecare<sup>SM</sup> medical policy is intended to serve only as a general reference resource regarding 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 Wholecare may provide coverage under the medical laboratory testing benefits of the Company's Medicaid products for medically necessary BCR-ABL1 (Philadelphia chromosome) testing.

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

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

## **Definitions**

**Prior Authorization Review Panel (PARP)** – A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

**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

**Fluorescence in Situ Hybridization (FISH)** – A cytogenetic technique that uses fluorescent probes that bind to only those parts of the chromosome with a high degree of sequence complementarity.

**Human Leukocyte Antigen (HLA) typing** – A method to determine how closely the tissues of one person match the tissues of another person. HLAs are proteins you inherit from your parents.

**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 of 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 leukemia in children. ALL affects only 20% of all leukemia 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 (Breakpoint Cluster Region-Abelson)** – 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:

- a. 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
- b. Quantitative - indicated for monitoring of disease for any individual positive for the BCR/ABL fusion gene by qualitative assay
- c. Qualitative – indicated in the initial evaluation for individuals known to have a positive FISH cytogenetic test for BCR/ABL

## **Procedures**

BCR-ABL1 for CML requires a Program Exception. The ordering physician must provide a supporting statement indicating why the requested therapy is medically necessary, and any alternative options have been, or are likely to be, ineffective, adversely affect individual compliance, or cause an adverse reaction (see the 'Governing Bodies Approval' section below).

BCR-ABL1 testing is considered medically necessary in the assessment of individuals with possible chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL).

1. BCR-ABL1 fusion gene testing is considered medically necessary to establish a diagnosis of CML when ANY of the following conditions are met:
  - A. When performing qualitative testing (blood or bone marrow) for the diagnosis of CML, since the information is necessary for subsequent quantitative testing of fusion gene messenger RNA transcripts; OR
  - B. When performing testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (qPCR) (blood or bone marrow) for monitoring CML treatment response and remission under ANY of the following situations:
    - 1) Baseline prior to initiation of treatment; OR
    - 2) At ANY of the following appropriate intervals during therapy:
      - a) Every three (3) months after initiating treatment; OR
      - b) After a complete cytogenetic response is reached ( $\text{BCR-ABL1 [IS]} \leq 1\%^2$ ), every three (3) months for two (2) years, then every three (3) to six (6) months; OR
      - c) If there is a 1-log increase in BCR-ABL1 transcript levels with MMR, qPCR can be repeated between one (1) to three (3) months; OR
  - C. Kinase domain point mutations (blood or bone marrow) to evaluate individuals for tyrosine kinase inhibitor resistance under ANY of the following conditions:
    - 1) There is a failure to reach response milestones; OR
    - 2) There is any sign of loss or response (defined as hematologic or cytogenetic relapse); OR
    - 3) There is a 1-log increase in BCR-ABL1 transcript level and loss of MMR; OR
    - 4) There is a progression of the disease to the accelerated or blast phase.

**Note:** BCR-ABL1 for CML (CPT codes 81206, 81207, & 81208) requires a Program Exception. The ordering physician must provide a supporting statement indicating why the requested therapy or device is medically necessary, and the alternative options have been or are likely to be ineffective, adversely affect individual compliance, or cause an adverse reaction.

2. BCR-ABL1 fusion gene testing is considered medically necessary to establish a diagnosis of ALL when ANY of the following conditions are met:
  - A. BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain (RT-PCR) for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission under ANY of the following situations:
    - 1) At baseline prior to initiation of treatment; OR
    - 2) At appropriate intervals during therapy; OR
    - 3) For ABL kinase domain point mutations for monitoring to evaluate individuals for tyrosine kinase inhibitor resistance under EITHER of the following situations:

- a) There is an inadequate initial response to treatment at three (3), six (6), and twelve (12) months; OR
  - b) At any time when there are signs of loss of response.
3. When BCR-ALB1 mutation testing is considered not medically necessary:
  - For all other conditions other than those listed above because the scientific evidence has not been established and therefore is not medically necessary.
  - The evaluation of ABL kinase domain single nucleotide variants for monitoring in advance signs of treatment failure or disease progression is considered experimental/investigational, and therefore, not medically necessary.
4. Post-payment Audit Statement

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare at any time pursuant to the terms of your provider agreement.
5. Place of Service

The proper place of service for the BCR/AB1 (Philadelphia Chromosome) genetic testing is typically in an outpatient setting.
6. Genetic Counseling

Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform individuals being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has previously evaluated the individual, and intends to see the individual after genetic testing has been performed:

  - 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 of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing
7. Related Policy
  - MP-010-MD-PA Testing for Genetic Disease

## **Governing Bodies Approval**

The BCR-ABL1 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.

The Centers for Medicare and Medicaid Services (CMS) has published the following guidance:

- Local Coverage Determination (LCD) Biomarkers for Oncology (L35396)
- Local Coverage Article (LCA) Billing and Coding: Biomarkers for Oncology (A52986)

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

As of March 2013, the TAG workgroup assigned genetic test BCR-ABL1 genetic testing for CML an Option # 2, specifically for CPT codes 81206, 81207, and 81208.

### **Program Exception**

BCR-ABL1 for CML requires a Program Exception. The ordering physician must provide a supporting statement indicating why the requested therapy is medically necessary, and any alternative options have been, or are likely to be, ineffective, adversely affect individual compliance, or cause an adverse reaction.

## **Summary of Literature**

There are various nucleic acid-based laboratory methods for the treatment of Philadelphia chromosome (Ph)-positive leukemia that can be used to detect the BCR-ABL1 fusion gene. This testing can be utilized to confirm a diagnosis for quantification of mRNA BCR-ABL1 transcripts during and after treatment; to monitor disease progression or remission and to identify ABL kinase domain point mutations related to drug resistance when there is inadequate reaction of loss of response to tyrosine kinase inhibitors or disease progression.

### **Chronic Myelogenous Leukemia (CML)**

CML accounts for 15%–20% of all adult leukemias. The Ph chromosome is the truncated chromosome 22 generated by the reciprocal translocation t(9;22)(q34;q11) and was first identified in 1960 in an individual with CML. Tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 protein are the most successful targeted therapy for Ph-positive leukemia. However, therapeutic resistance and disease progression are the current barriers to improve the prognosis of individuals with Ph-positive leukemia (Kang, et al., 2016).

CML is caused by a mutation created when a portion of chromosome 9 and a portion of chromosome 22 break off and trade places. The result is a fused gene called BCR-ABL1 and the abnormal chromosome 22 called the Philadelphia chromosome. CML is a type of myeloproliferative neoplasm (MPN). MPNs are a group of blood cancers that begin in the myeloid progenitor cells. MPNs produce too many blood cells making it difficult for blood to process normally (NCCN, 2023).

The presence of the Ph results in individuals with different leukemia phenotypes having substantially different prognoses. In addition, other concurrent genomic abnormalities are more common in leukemia cells with Ph than in those without. These genomic variations, in combination with BCR-ABL1 transcripts, play an important role during leukemogenesis (Kang, et al., 2016).

Typically, CML has three clinical phases: an initial chronic phase, during which the disease process is easily controlled; then a transitional and unstable course (accelerated phase); and, finally, a more aggressive course (blast crisis), which is usually fatal. In all three phases, supportive therapy with transfusions of red blood cells or platelets may be used to relieve symptoms and improve quality of life (Besa, Grethlein et al, 2021).

The chronic phase varies in duration, depending on the maintenance therapy used: it usually lasts 2-3 years with hydroxyurea (Hydrea) or busulfan therapy, but it may last for longer than 9.5 years in individuals who respond well to interferon-alfa therapy. Furthermore, the advent of tyrosine kinase inhibitor (TKI) therapy has dramatically improved the duration of hematologic and, indeed, cytogenetic remissions. For most individuals with chronic-phase CML who are treated with TKIs, median survival is expected to approach normal life expectancy (Besa, Grethlein et al, 2021).

In 2010, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on BCR-ABL1 pharmacogenetic testing for tyrosine kinase inhibitors in CML. Thirty-one publications of BCR-ABL1 testing met the eligibility criteria and were included in the review (20 of dasatinib, 7 of imatinib, 3 of nilotinib, and 1 with various TKIs). The report concluded that the presence of any BCR-ABL1 mutation does not predict differential response to TKI therapy, although the presence of the T315I mutation uniformly predicts TKI failure. However, during the public comment period the review was strongly criticized by respected pathology organizations for lack of attention to several issues that were subsequently insufficiently addressed in the final report. Importantly, the review grouped together studies that used kinase domain mutation screening methods with those that used targeted methods, and grouped together studies that used mutation detection technologies with very different sensitivities. The authors dismissed the issues as related to analytic validity and beyond the scope of the report. However, in this clinical scenario assays with different intent (screening vs. targeted) and assays of very different sensitivities may lead to different clinical conclusions, so an understanding of these points is critical.

Mutations in the kinase domain of BCR-ABL are the leading cause of acquired imatinib resistance. Although mutations have been identified in more than 30 different amino acids, the highest degree of resistance was associated with single-point mutation T315I of the ABL gene in the BCR-ABL fusion transcript. Early detection of T315I mutation of CML patient in therapy or pre-therapy could allow alternative treatment before resistance is detected cytogenetically or before disease progression become evident.

The National CML Society guidelines indicate that cytogenetic testing be performed at diagnosis, three months, six months and every six months until complete cytogenetic response has been achieved and

confirmed. Following confirmation, cytogenetic testing should be performed every 12 months if regular molecular monitoring cannot be assured. The desired responses to first-line treatment according to NCCN guidelines are as follows:

- 3 months: BCR-ABL1 transcripts  $\leq 10\%$  by qPCR
- 6 months: BCR-ABL1 transcripts  $\leq 10\%$  by qPCR
- 12 months:  $\leq 1\%$  *BCR-ABL1*
- 15 months:  $\leq 1\%$  *BCR-ABL1*
- After BCR-ABL1 (IS)  $\leq 1\%$  ( $> 0.1\% - 1\%$ ) has been achieved, every 3 months for 2 years and every 3–6 months thereafter; if there is 1-log increase in *BCR-ABL1* transcript levels with major molecular response, qPCR should be repeated in 1-3 months (Besa, Grethlein et al, 2021).

The goal of CML treatment is return blood counts to normal (hematologic response) and to eliminate or reduce the number of leukemia cells, as determined by the disappearance of the Philadelphia chromosome (complete cytogenetic response) and a decrease in the level of BCR-ABL.

For individuals with disease resistance to TKI therapy, it is important to identify potential ABL mutations that can underlie the observed resistance to treatment. A panel of experts from the European LeukemiaNet published recommendations for the analysis of ABL kinase domain mutations in individuals with CML, and the treatment options according to the presence of different ABL mutations (Soverini, et al., 2011).

#### NCCN Clinical Practice Guidelines

The initial recommended CML workup includes:

- History & physical, including spleen size by palpation (cm below costal margin)
- CBC with differential
- Chemistry profile
- Bone marrow aspirate and biopsy for morphologic review and cytogenetic evaluation
- Quantitative RT-PCR (qPCR) using International Scale (IS) for BCR-ABL1 (blood)
- Hepatitis B panel

Quantitative RT-PCR should be done at initial workup to establish the presence of quantifiable BCR-ABL1 mRNA transcripts. qPCR, usually done on peripheral blood, is the most sensitive assay available for the measurement of BCR-ABL1 mRNA and it can detect one CML cell in a background of  $> 100,000$  normal cells. qPCR results can be expressed in various ways, for instance as the ratio of BCR-ABL1 transcript number to the number of control gene transcripts. An International Scale (IS) has been established to standardize the molecular monitoring with qPCR across different laboratories with the use of one of three control genes (BCR, ABL1, or GUSB) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline. In recent years, IS has become the gold standard of expressing qPCR values. Qualitative RT-PCR for the deletion of atypical BCR-ABL1 transcripts should be considered if there is discordance between FISH and qPCR results. BCR-ABL1 transcripts in the peripheral blood at very low levels (1-10 out of  $10^8$  peripheral blood leukocytes) can be detected in approximately 30% of normal individuals, and the incidence of this increases with age. The risk of developing CML for these individuals is extremely low, and neither continued monitoring nor therapy are indicated.

Individuals with disease resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting, taking into account BCR-ABL1 mutation status. Individuals with disease resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be



treated with an alternate TKI (other than imatinib) in the second-line setting, taking into account BCR-ABL1 mutation status. The durability of these responses is frequently limited. There are no standardized qPCR assays for monitoring molecular response to TKI therapy in patients with atypical BCR-ABL1 transcripts.

### **Acute Lymphoblastic Leukemia (ALL)**

ALL is a fast-growing cancer that starts in lymphocytes, a type of white blood cell. In ALL, bone marrow produces too many immature lymphocytes called lymphoblasts. Lymphoblasts can crowd out other blood cells causing blood to not function properly. Treatment depends on the type of ALL, age at diagnosis, and other factors (NCCN, 2021).

The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths estimated for 2021. Risk factors for developing ALL include older age ( $\geq$  years), exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome. Although rare, other genetic conditions have been categorized as a risk factor for ALL and include Li-Fraumeni syndrome, neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome, and ataxia telangiectasia (NCCN, 2021).

ALL is classified into smaller groups (subtypes) based on certain features of the leukemia cells. There are two broad subtypes based on the category of lymphocyte the leukemia cells originate from, which is called cell subtypes. There are many ALL cell subtypes based on immunophenotype. The two main cell subtypes are B-cell ALL and T-CELL ALL (NCCN, 2023).

In ALL there are also cytogenetic subtypes based on the type of abnormal changes found in the chromosomes of the leukemia cells. Many different types of chromosome changes occur in ALL. The two main cytogenetic subtypes used for treatment planning are based on the presence or absence of the Philadelphia chromosome. Ph-positive ALL is the subtype of ALL with the abnormal Philadelphia chromosome which is more in adults than children. The Ph-negative is the subtype of ALL where the Philadelphia chromosome is not present which is more common in children than adults (American Cancer Society, 2018).

ALL is the most common childhood tumor and represents 75 to 80% of acute leukemias in children. Approximately 20% of adults with leukemia are diagnosed with ALL. Survival rates for patients with ALL are improving due to advances in the understanding of molecular genetics of the disease, incorporation of risk-adapted therapy and new target agents. While cure rates in children are about 80%, the long term prognosis among adults range between 30 – 40%. The lower cure rates in adults is the result of different subtypes in adults, including the BCR-ABL fusion gene. The infusion gene is less common in childhood ALL than in adults with ALL (NIH, 2023).

TKIs are combined with chemotherapy to treat lymphoblastic leukemias and lymphomas (ALL/LBL) that have t (9; 22)/BCR-ABL rearrangements. ABL kinase domain mutations, particularly T315I, F317L, and Y253H, are frequently present in ALL/LBL patients who lack initial response or who relapse. Identification of the particular resistance-causing mutation(s) can help guide therapy for such patients (Jones, et al. 2009).

Resistance to one or more TKIs during treatment or resistance to induction therapy can lead to a poor prognosis. Individuals with Ph+ALL frequently relapse on imatinib with the acquisition of BCR-ABL kinase domain mutations. In 2014, Soverini and colleagues looked at laboratory data and analyzed the changes

that second-generation TKIs brought in mutation frequency and type. Data were analyzed for 272 individuals. A total of 189 individuals were reported to be resistant to imatinib, 131 were found to be positive for the BCR-ABL kinase domain mutation. Ninety-eight individuals had developed resistance to secondary TKIs and 76 of those individuals were found to be positive for BCR-ABL kinase domain mutations. Of these 98 individuals, 93 were resistant to dasatinib as second-line therapy. Of the 93 who relapsed while on second-line dasatinib, 74 showed BCR-ABL kinase domain mutations. Of the mutations found, T315-I was the most frequent and accounted for 70% of the mutations (Soverini, et al., 2014).

According to NCCN guidelines, the initial workup for individuals with ALL should include:

- A thorough medical history and physical exam
- Lab and imaging studies (where applicable). Lab studies include a complete blood count (CBC) with platelets and differential, a blood chemistry profile, liver function tests, a disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time)
- A tumor lysis syndrome (TLS) panel. Other recommended tests include hepatitis B/C, HIV, and cytomegalovirus (CMV) antibody evaluations. Female patients should undergo pregnancy testing and all male patients should be evaluated for testicular involvement disease, including a scrotal ultrasound as indicated; testicular involvement is especially common in cases of T-ALL. CT scans of the neck, chest, abdomen, and pelvis with IV contrast are recommended as indicated by symptoms, and if any extramedullary involvement is suspected, a PET/CT may be considered for diagnosis and follow-up.

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. Peripheral blood may be substituted for bone marrow provided there is a significant amount circulating disease, with the NCCN ALL Panel suggesting a general guide of greater than or equal to 1,000 circulating lymphoblastic per microliter. The WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease (American Cancer Society, 2018).

After completion of the ALL treatment regimen (including maintenance therapy), the panel recommends surveillance at regular intervals to assess disease status. During the first year after completion of therapy, individuals should undergo a complete physical exam and blood tests (CBC with differential). Liver function tests should be performed until normal values are achieved. An assessment of bone marrow aspirate can be considered as clinically indicated at a frequency of 3 to 6 months for the first 5 years; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be carried out. If relapse is suspected, a full workup should be considered. For Ph-positive ALL, periodic quantification of the BCR-ABL1 transcript should be determined (NCCN, 2023).

## **Coding Requirements**

### Procedure Codes

<b>CPT Code</b>	<b>Description</b>
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
0016U	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
0040U	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

### Diagnosis Codes

<b>ICD-10 Code</b>	<b>Description</b>
C91.00	Acute lymphoblastic leukemia, not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C92.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C92.11	Chronic lymphocytic leukemia of B-cell type in remission
C92.12	Chronic lymphocytic leukemia of B-cell type in relapse
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.21	Atypical chronic myeloid leukemia, BCR/ABL-negative, in remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
C92.90	Myeloid sarcoma, not having achieved remission
C92.91	Myeloid sarcoma, in remission
C92.92	Myeloid sarcoma, in relapse

## **Reimbursement**

Participating facilities will be reimbursed per their Highmark Wholecare<sup>SM</sup> contract.

## **Reference Sources**

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology, Chronic Myeloid Leukemia. Version 1.2024. August 1, 2023. Accessed on October 17, 2023.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. Version 3.2023. October 9, 2023. Accessed on October 17, 2023.

Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD) Biomarkers for Oncology (L35396). Original Effective date October 1, 2015. Revision Effective date December 13, 2020. Accessed on October 21, 2024.

Pennsylvania Health Choices. Managed Care Operations Memorandum, Technology Assessment Group (TAG) Coverage Decisions. OPS#03/2013-003, Option #2. Accessed on October 21, 2024.

Soverini S, Hochhaus A, Nicolini FE, et al. 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*. August 2011. Accessed on September 15, 2021.

Soverini S, De Benedittis C, Papayannidis C, et al. Drug resistance and BCR-ABL kinase domain mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia from the imatinib to the second-generation tyrosine kinase inhibitor era: The main changes are in the type of mutations, but not in the frequency of mutation involvement. *Cancer*. 2014. Accessed on September 15, 2021.

Besa E, Grethlein SJ et al., Chronic Myelogenous Leukemia (CML). *Medscape*. Updated May 23, 2021. Accessed on September 15, 2021.

Centers for Medicare and Medicaid Services (CMS). Local Coverage Article (LCA) Billing and Coding: Biomarkers for Oncology (A52986). Original Effective date October 1, 2015. Revision Effective date August 7, 2023. Accessed on October 21, 2024.

The American Cancer Society. Tests for Acute Lymphocytic Leukemia (ALL). October 17, 2018. Accessed on October 17, 2023.

National Institutes of Health (NIH). National Cancer Institute. Childhood Acute Lymphoblastic Leukemia Treatment. Updated on October 12, 2023. Accessed on October 17, 2023.

Kang ZJ, Liu YF, Xu LZ, et al. The Philadelphia chromosome in leukemogenesis. *Chin J Cancer*. May 27, 2016. Accessed on October 17, 2023.