CLINICAL MEDICAL POLICY	
Policy Name:	BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
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Responsible Department(s):	Medical Management
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 12

Policy History

Date	Action
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℠ 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 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 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 patient positive for the BCR/ABL fusion gene by qualitative assay
c. Qualitative – indicated in the initial evaluation for patients known to have a positive FISH cytogenetic test for BCR/ABL

Procedures

BCR-ABL1 testing is considered medically necessary in the assessment of individuals with 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. 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. 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 appropriate intervals during therapy:
         a) Every three months after initiating treatment; OR
         b) After complete cytogenetic response is reached (BCR-ABL1 [IS] $\leq 1\%^2$), every three months for 2 years, then every three to six months; OR
         c) If there is a 1-log increase in BCR-ABL1 transcript levels with MMR, qPCR can be repeated in 1-3 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.

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 Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission under EITHER of the following situations:
        1) At baseline prior to initiation of treatment; OR
        2) At appropriate intervals during therapy; OR
        3) 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 not considered medically necessary
    - For all other conditions other than those listed above, scientific evidence has not been established and therefore 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 patient 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 patient, and intends to see the patient 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 or device is medically necessary, and the alternative options have been or are likely to be ineffective, adversely affect patient compliance, or cause an adverse reaction.

Summary of Literature

For the treatment of Philadelphia chromosome (Ph)-positive leukemia, there are various nucleic acid-based laboratory methods 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 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, 2021).

More than 90% of patients with CML have a proliferation of cells in their bone marrow and blood. The cells show a value of, t(9:22) (q34;q11.2) which is often called the Philadelphia Translocation. The Philadelphia Translocation is also observed in 3% of children and 20% of adults with Acute Lymphoblastic Leukemia (ALL) and in 1% of patients with Acute Myeloid Leukemia (AML). The balanced translocation between chromosomes 9 and 22 involves the Abelson (ABL) oncogene at 9q34 and the breakpoint cluster region (BCR) at 22q11.2.

In CML, the hybrid BCR/ABL gene is always present and the abnormal chimeric protein has increased tyrosine kinase activity. In a minority of cases, the breakpoint in the BCR gene can occur in a minor region. Fluorescent in Situ Hybridization (FISH) methods permit visualization of BCR/ABL fusion in individual interphase and metaphase cells. A tricolor, dual fusion FISH method detects BCR/ABL fusion in cells, deletion on derivative chromosome 9 and chromosome 22, and deletion of arginisosuccinate synthetase (ASS) gene which is located at chromosome 9q34. Deletion of ASS is an indicator of a subclone of cells within the Philadelphia positive cells that may be changing or mutating. This indicator has been associated with poor prognosis.

In classic CML, the presence of the translocation or the BCR/ABL fusion establishes the diagnosis and predicts the transformation into blast crisis (accelerated phase). FISH confirmation or exclusion of CML in suspected cases is critical to allow tailored therapy. Testing must quantify the abnormal cells before and after treatment to help assess effectiveness of therapy. Low levels of abnormal cells predict relapse early and lead to revision of therapy. With conventional cytogenetics methods, evidence of translocation or low levels of mosaicism may be missed.

Fluorescence in situ hybridization (FISH) studies on peripheral blood will confirm the presence of a BCR-ABL gene but can also be designed to detect a possible deletion in the chromosome 9. Neutrophil alkaline phosphatase is no longer routinely measured. HLA typing for the patient and family members may prove useful when the patient is aged less than 65 years. The clinical significance of such altered transcripts is unclear and reporting such mutations is not recommended by the U.S. Association for Molecular Pathology.

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 patients 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 patients 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 ≤10% by qPCR
- 6 months: BCR-ABL1 transcripts ≤10% by qPCR
- 12 months: ≤1% *BCR-ABL1*
- 15 months: ≤ 1% *BCR-ABL1*
- After BCR-ABL1 (IS) ≤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 (compete cytogenetic response) and a decrease in the level of BCR-ABL.

For patients 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 patients 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.

Patients 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. Patients 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 (≥ 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.

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.

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.

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.

According to NCCN guidelines, the initial workup for patients with ALL should include a thorough medical history and physical exam, along with 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), and a tumor lysis syndrome (TLS) panel. Other recommended tests include hepatitis B/C, HIV, and cytomgelovirus (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.

Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), and interphase fluorescence in situ hybridization (FISH) assays that include probes capable of detecting the genetic abnormalities and/or RT-PCR testing, using qualitative or quantitative methods, to measure transcript sizes (ie, p190 vs. p210) of BCR-ABL1 in B-ALL. If samples are BCR-ABL1/Ph-negative or Ph-like, comprehensive testing by next-generation sequencing (NGS) for other gene fusions and pathogenic mutations associated with Ph-like ALL is recommended. In cases of aneuploidy or failed karyotype, additional assessment may include chromosomal microarray (CMA)/array comparative genomic hybridization (aCGH).

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, patients 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.

Coding Requirements

Procedure Codes

CPT Code	Description
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

ICD-10 Code	Description
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 myeloid leukemia, BCR/ABL positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL positive, 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 leukemia, unspecified, not having achieved remission
C92.91	Myeloid leukemia, unspecified, in remission
C92.92	Myeloid leukemia, unspecified in relapse

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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