CLINICAL MEDICAL POLICY

Policy Name:	BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
Policy Number:	MP-017-MD-PA
Approved By:	Medical Management
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Disclaimer

Gateway Health℠ (Gateway) 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:

Gateway Health ® provides coverage under the medical laboratory testing benefits of the Company's Medicaid products for medically necessary 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 warrants 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 – 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

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:

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

1) The following medical necessity criteria must be met:
   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:
      - Baseline prior to initiation of treatment; AND
      - 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:

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- There is inadequate initial response to treatment at three, six and 12 months; OR
- Any sign of loss or response; OR
- There is progression of the disease to accelerate or blast phase

ALL

- Determining the qualitative presence of the BCR-ABL1 fusion gene is necessary to establish a diagnosis of ALL
- 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:
    - At baseline prior to initiation of treatment; and
    - At appropriate intervals during therapy
    - Optimal timing of monitoring remains unclear
- ABL kinase domain point mutations for monitoring are medically necessary to evaluate patients for tyrosine kinase inhibitor resistance when:
    - There is inadequate initial response to treatment at three six and 12 months; OR
    - 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 Gateway Health Plan® 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 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

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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.

b. Additional information available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

Summary of Literature

For the treatment of Philadelphia chromosome (Ph)-positive leukemias, 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 for identification of ABL kinase domain point mutations related to drug resistance when there is inadequate response of loss of response to tyrosine kinase inhibitors or disease progression.

Chronic Myelogenous Leukemia (CML)

It is always important to confirm that the suspected diagnosis of Ph-positive CML. Essential investigations include a full blood count ideally with a 1000 cell differential performed by microscopy, a bone marrow aspirate and trephine biopsy together with bone marrow cytogenetics and real-time quantitative reverse transcriptase (RQ-PCR) for *BCR-ABL* transcripts. Fluorescence in situ hybridization (FISH) studies on a peripheral blood will confirm the presence of a BCR-ABL gene but can also be designed to detect a possible deletion in the 9 chromosome. Neutrophil alkaline phosphatase is no longer routinely measured. HLA typing for the patient and family members may prove useful if the patient is aged less than 65 years.

More than 90% of patients with Chronic Myelogenous Leukemia (CML) have a proliferation of cells in their bone marrow and blood which show t(9:22)(q34;q11.2) – often called the Philadelphia Translocation. This translocation is also observed in 3% of children and 20% of adults with Acute Lymphoblastic Leukemia (ALL), as well as 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.

The 2016 National Comprehensive Cancer Network (NCCN) practice guidelines regarding chronic myelogenous leukemia (CML) recommended methods for diagnosis and treatment management of CML, including *BCR-ABL1* tests for diagnosis, monitoring, and *ABL* kinase domain mutations. Other types of mutations in addition to point mutations can be detected in the *BCR-ABL1* gene, including alternate splicing, insertions, deletions and/or duplications. The clinical significance of such altered transcripts is unclear and reporting such mutations is not recommended by the U.S. Association for Molecular Pathology.

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In 2010, the Agency for Healthcare Research and Quality 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, 3 months, six months and every 6 months until complete cytogenetic response has been achieved and confirmed. Following confirmation, cytogenetic testing should be performed every 12months if regular molecular monitoring cannot be assured.

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.

Patients with disease resistant 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)

Acute Lymphoblastic Leukemia (ALL)
ALL is classified into smaller groups (subtypes) based on certain features of the leukemia cells. There are two broad subtypes based on type of lymphocyte the leukemia cells originate from 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 chromosomes changes occur in ALL. The Philadelphia chromosome is an abnormal chromosome found in some people with ALL which is formed when pieces of chromosomes 9 and 22 translocate. 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.

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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 compared to 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.

For patients with less than a complete response to induction or have relapsed disease not participating in a clinical trial, the National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology for Acute Lymphoblastic Leukemia recommends treatment with multi-agent chemotherapy combined with an alternative TKI (that is, different from the TKI used as part of induction therapy). The choice of TKI would be directed by BCR-ABL kinase domain mutations. NCCN adopted recommendations for treatment options based on ABL mutation status for CML developed by the European LeukemiaNet. Based on these recommendations, dasatinib (if not used for induction) could be considered for individuals with relapsed/refractory Ph+ disease with mutations Y253H, E255K/V, or F359V/C/I. For individuals with relapsed/refractory disease with BCR-ABL mutations V299L, T315A, or F317L/V/I/C, nilotinib could be considered. Bosutinib has shown activity against several of the BCR-ABL mutations (E255K/V, F317L/V/I/C, F359V/C/I, T315A, Y253H), but not T315-I. More recently, additional TKI agents have been developed which have shown promising results in the management of those individuals with T315-I mutation. Ponatinib has been shown to be active against several of the BCR-ABL mutations in addition to T315-I (NCCN, 2014).

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

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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
81401	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)
81403	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)

Diagnosis Codes

ICD-10 Diagnosis Codes	Description
C91.0	Acute lymphoblastic leukemia (ALL)
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

Monitoring Schedule

Response Level	Definition	Monitoring Frequency/Schedule
Hematologic *Complete Hematologic Response (CHR)*	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)**.	**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.
Cytogenetic *Complete (CCyR) Partial (PCyR) Minor Minimal*	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. Minor: 35 - 65%. Minimal: 66 - 95%.	**At diagnosis**, **3 months**, and **6 months**, then **every 6 months** until CCyR has been achieved and confirmed.

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Response Level	Definition	Monitoring Frequency/Schedule
	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. 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).	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 *Complete Molecular Response (CMR)* *Major Molecular Response (MMR)*	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). 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. 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 LeukemiaNet Guidelines for CML.

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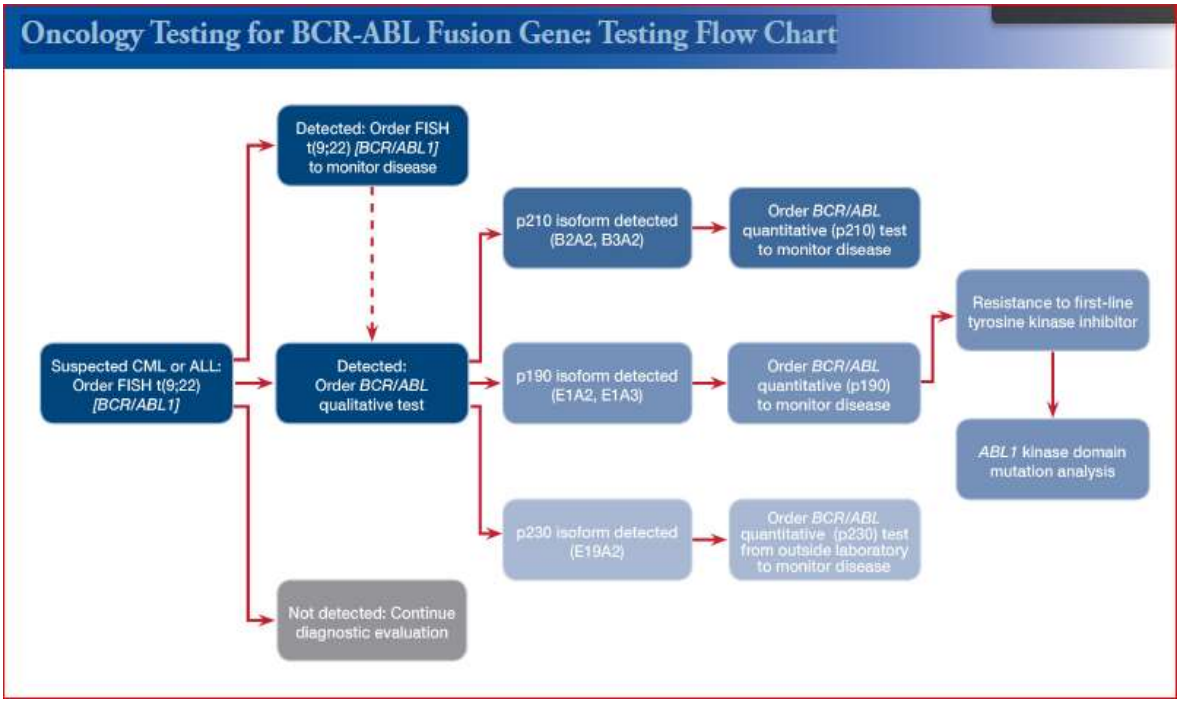
Timing of Cytogenetic and Molecular Monitoring	
At diagnosis	CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type)
During treatment	RQ-PCR every 3 months until MMR has been achieved, then every 3 to 6 months and/or CBA at 3, 6, and 12 months until CCyR has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

From the Leukemia-Net. Org. Available at: http://www.leukemia-net.org/content/leukemias/cml/recommendations/e8078/infoboxContent10432/PocketCard_UPDATE2013_English.pdf.

Example BCR/ABL Testing Flow Chart



Cincinnati Children's Diagnostic Laboratories

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