MASSACHUSETTS

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Medical Policy

BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

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Policy Number: 612

BCBSA Reference Number: 2.04.85
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

CML

BCR/ABL1 qualitative testing for the presence of the fusion gene may be **MEDICALLY NECESSARY** for diagnosis of chronic myeloid leukemia.

BCR/ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline prior to initiation of treatment and at appropriate intervals during therapy may be **MEDICALLY NECESSARY** for monitoring of chronic myeloid leukemia treatment response and remission.

Testing is appropriate at baseline before the start of imatinib treatment. Testing is appropriate every 3 months when the patient is responding to treatment. After a complete cytogenetic response is achieved, testing is appropriate every 3 months for 3 years, and then every 3-6 months thereafter. Without attainment of a complete cytogenetic response, continued monitoring at 3-month intervals is recommended.

Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be **MEDICALLY NECESSARY** when there is inadequate initial response to treatment or any sign of loss of response; and/or when there is progression of the disease to the accelerated or blast phase. Inadequate initial response to tyrosine kinase inhibitors is defined as failure to achieve complete hematologic response at 3 months, only minor cytological response at 6 months or major (rather than complete) cytogenetic response at 12 months.

Loss of response to tyrosine kinase inhibitors is defined as hematologic relapse, cytogenetic relapse or 1 log increase in *BCR-ABL1* transcript ratio and therefore loss of major molecular response.

Evaluation of *ABL* kinase domain point mutations is **INVESTIGATIONAL** for monitoring in advance of signs of treatment failure or disease progression.

ALL
BCR/ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR) at baseline prior to initiation of treatment and at appropriate intervals during therapy may be **MEDICALLY NECESSARY** for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.

Evaluation of *ABL* kinase domain point mutations to evaluate patients for tyrosine kinase inhibitor resistance may be **MEDICALLY NECESSARY** when there is inadequate initial response to treatment or any sign of loss of response.

Evaluation of *ABL* kinase domain point mutations is **INVESTIGATIONAL** for monitoring in advance of signs of treatment failure or disease progression.

Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link below.

ABL1 (abl proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain (CPT 81170)

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for M**edicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue[SM]	Prior authorization is **not required**.
Medicare PPO Blue[SM]	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81170	ABL1 (abl proto-oncogene 1, non-receptor tyrosine kinase) (eg, 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
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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

ICD-10-CM Diagnosis Codes

ICD-10-CM Diagnosis codes:	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

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

Description

In the treatment of Philadelphia chromosome (Ph)-positive leukemias, various nucleic acid-based laboratory methods may be used to detect the *BCR-ABL1* fusion gene for confirmation of the diagnosis; for quantifying 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 or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

Background

Disease

CML
Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic stem cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within 3 to 5 years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, very high or very low platelet counts, etc. From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow.

ALL
Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL is the most common childhood tumor, and represents 75% to 80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The median age at diagnosis is 14 years; 60% of patients are diagnosed at younger than 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past several decades, primarily in children, largely due to advances in the understanding of the molecular genetics of the disease, the incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of ~80%. The long-term prognosis among adults is poor, with cure rates of 30% to 40%, explained, in part, by different subtypes among age groups, including the *BCR-ABL* fusion gene, which has a poor prognosis and is much less common in childhood ALL, as compared with adult ALL.

Disease genetics
Ph-positive leukemias are characterized by the expression of the oncogenic fusion protein product BCR-ABL1, resulting from reciprocal translocation between chromosomes 9 and 22. This abnormal fusion gene characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as BCR-ABL1, are more common. In ALL, the Ph is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is generally associated with acute lymphoblastic leukemia, while p210 is most often seen in CML. The product of *BCR-ABL1* is also a functional tyrosine kinase; the kinase domain of the BCR-ABL protein is the same as the kinase domain of the normal ABL protein. However, the abnormal BCR-ABL protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Treatment and response and minimal residual disease
Imatinib (Gleevec®) was originally developed to specifically target and inactivate the ABL tyrosine kinase portion of the BCR-ABL1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in “durable responses in [a] large proportion of the patients with a decreasing rate of relapse.” As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percent of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (CCyR; 0% Ph-positive metaphases) is expected by 6 to 12 months after initial treatment with the TKI imatinib. It has been well established that most “good responders” that are considered to be in morphologic remission but relapse may still have considerable levels of leukemia cells, referred to as minimal residual disease (MRD.) Among children with ALL who achieve a complete response (CR) by morphologic evaluation after induction therapy, approximately 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD

detection include flow cytometry (which affords a sensitivity of MRD detection of 0.01%), or polymerase chain reaction (PCR)–based analyses (Ig and T-cell receptor gene rearrangements or analysis of BCR-ABL transcripts), which are the most sensitive method of monitoring treatment response, with a sensitivity of 0.001%. Ig and T-cell receptor gene arrangement analysis is applicable for most ALL patients, whereas PCR analysis of BCR-ABL transcripts is applicable only in Ph-positive patients. With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60% to 80% of patients achieving complete remission, significantly lower than that achieved in Ph-negative ALL. The inclusion of TKIs to frontline induction chemotherapy has improved CR rates, exceeding 90%.

Resistance
Imatinib treatment does not usually result in complete eradication of malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. In addition, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. The molecular basis for resistance is explained in the following section. When the initial response to treatment is inadequate or there is a loss of response, resistance mutation analysis is recommended to support a diagnosis of resistance (based on hematologic or cytogenetic relapse) and to guide the choice of alternative doses or treatments.

Structural studies of the ABL-imatinib complex have resulted in the design of second-generation ABL inhibitors, including dasatinib (Sprycel®) and nilotinib [Tasigna®), which were initially approved by the U.S. Food and Drug Administration (FDA) for treatment of patients resistant or intolerant to prior imatinib therapy. More recently, trials of both agents in newly diagnosed chronic phase patients showed that both are superior to imatinib for all outcomes measured after 1 year of treatment, including CCyR (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis. Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. On June 17, 2010, FDA approved nilotinib for the treatment of patients with newly-diagnosed chronic phase CML. Dasatinib was approved on October 28, 2010, for the same indication.

For patients with increasing levels of *BCR-ABL1* transcripts, there is no strong evidence to recommend specific treatment; possibilities include continuation of therapy with dasatinib or nilotinib at the same dose, imatinib dose escalation from 400 mg to 800 mg daily, as tolerated or therapy change to an alternate second-generation TKI are all options.

Molecular resistance
Resistance is most often explained at the molecular level by genomic instability associated with the creation of the abnormal *BCR-ABL1* gene, usually resulting in point mutations within the *ABL1* gene kinase domain that affects protein kinase-TKI binding. *BCR-ABL1* kinase domain (KD) point mutations account for 30% to 50% of secondary resistance. At least 58 different KD mutations have been identified in CML patients. The degree of resistance depends on the position of the mutation within the KD (ie, active site) of the protein. Some mutations are associated with moderate resistance and are responsive to higher doses of TKIs, while other mutations may not be clinically significant. Two mutations, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance. The T315I mutation is relatively common at frequencies ranging from 4% to 19%, depending on the patient population; it is more common in patients with advanced phase CML than in patients with early chronic phase CML.

Compared with imatinib, fewer mutations are associated with resistance to dasatinib or nilotinib. For example, Guilhot et al and Cortes et al studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell *BCR-ABL1* mutations. However, neither dasatinib nor nilotinib are effective against resistant clones with the T315I mutation, and new agents and treatment strategies are in development for patients with T315I resistance.

In a recent follow-up study of nilotinib by le Coutre et al, 137 patients with accelerated phase CML were evaluated after 24 months. Sixty-six percent of patients maintained major cytogenetic responses at 24 months. The estimates of overall and progression-free survival rates at 24 months were 70% and 33%, respectively. Grade 3/4 neutropenia and thrombocytopenia were each observed in 42% of patients.

Rarely, other acquired cytogenetic abnormalities such as *BCR-ABL* gene amplification and protein overexpression have also been reported. Resistance unrelated to kinase activity may result from additional oncogenic activation or loss of tumor suppressor function, and may be accompanied by additional karyotypic changes.

Summary

CML

Extensive clinical data have led to the development of congruent recommendations and guidelines developed both in North America and in Europe concerning the use of various types of molecular tests relevant to the diagnosis and management of chronic myelogenous leukemia (CML). These tests are also useful in the accelerated and blast phases of this malignancy. Appropriate uses are summarized as follows:

Diagnosis: Although CML is diagnosed primarily by clinical and cytogenetic methods, qualitative molecular testing is needed to confirm the presence of the *BCR-ABL1* fusion gene, particularly if the Philadelphia chromosome (Ph) was not found, and to identify the type of fusion gene, as this information is necessary for subsequent quantitative testing of fusion gene messenger RNA transcripts. If the fusion gene is not confirmed, then the diagnosis of CML is called into question.

Monitoring during treatment with tyrosine kinase inhibitors (TKIs): quantitative determination of *BCR-ABL1* transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment. Evaluation of trial samples has consistently shown that the degree of molecular response correlates with risk of progression. In addition, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising *BCR-ABL1* transcript levels predict treatment failure and the need to consider a change in management. Quantitative polymerase-chain reaction (PCR)-based methods and international standards (IS) for reporting have been recommended and adopted for treatment monitoring.

Treatment failure: the presence of ABL kinase domain point mutations are associated with treatment failure; a large number of mutations have been detected, but extensive analysis of trial data with low-sensitivity mutation detection methods has identified a small number of mutations that are consistently associated with treatment failure with specific TKIs; guidelines recommend testing for, and using information regarding these specific mutations in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography (DHPLC) screening to reduce the number of samples that need to be sequenced. Targeted methods that detect the mutations of interest for management decisions are also acceptable if designed for low sensitivity. High sensitivity assays are not recommended.

While the existing evidence is associational in nature, the body of evidence that has been accumulated and the consequences of the management decisions involved, along with international agreement on recommendations of the use of molecular assays, support the medical necessity of the use of the assays as described. Other uses and other types of assays are considered investigational.

ALL

Diagnosis: the presence of the *BCR-ABL1* fusion gene is not necessary to establish a diagnosis of ALL. However, before initiation of therapy, identification of the *BCR-ABL* transcript is necessary for risk stratification and quantification to establish baseline levels for subsequent monitoring of response during treatment.

Monitoring during treatment with TKIs: quantitative determination of *BCR-ABL1* transcript levels during treatment allows for a very sensitive determination of the degree of patient response to treatment.

Evaluation of trial samples has consistently shown that the degree of molecular response correlates with risk of progression. For ALL, the optimal timing remains unclear and depends upon the chemotherapy regimen used.

Treatment failure: Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL who are receiving a TKI, a rise in the *BCR-ABL* level while in hematologic CR or clinical relapse warrants mutational analysis.

Policy History

Date	Action
9/2018	Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000) added. 9/2018
4/2018	Clarified coding information.
11/2017	New references added from BCBSA National medical policy.
4/2016	New references added from BCBSA National medical policy.
1/2016	Clarified coding information.
8/2014	BCBSA National medical policy review. New medically necessary and investigational indications described; title changed to include ALL. Coding information clarified. Effective 8/1/2014.
7/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
8/2013	BCBSA National medical policy review. New policy describing medically necessary and investigational indications. Effective 8/1/2013.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* Oct 1 2002;100(7):2292-2302. PMID 12239137
2. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program.* Dec 2012;2012:389-396. PMID 23233609
3. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Chronic Myelogenous Leukemia. Version 1.2018. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed September 18, 2017.
4. Fielding AK, Zakout GA. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Curr Hematol Malig Rep.* Jun 2013;8(2):98-108. PMID 23475624
5. Campana D. Should minimal residual disease monitoring in acute lymphoblastic leukemia be standard of care? *Curr Hematol Malig Rep.* Jun 2012;7(2):170-177. PMID 22373809
6. Jones D, Kamel-Reid S, Bahler D, et al. Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. *J Mol Diagn.* Jan 2009;11(1):4-11. PMID 19095773
7. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med.* Jun 17 2010;362(24):2251-2259. PMID 20525993
8. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* Jun 17 2010;362(24):2260-2270. PMID 20525995
9. Mughal TI, Goldman JM. Emerging strategies for the treatment of mutant Bcr-Abl T315I myeloid leukemia. *Clin Lymphoma Myeloma.* Mar 2007;7(Suppl 2):S81-84. PMID 17382017

10. von Bubnoff N, Manley PW, Mestan J, et al. Bcr-Abl resistance screening predicts a limited spectrum of point mutations to be associated with clinical resistance to the Abl kinase inhibitor nilotinib (AMN107). *Blood.* Aug 15 2006;108(4):1328-1333. PMID 16614241
11. Piccaluga PP, Martinelli G, Rondoni M, et al. Advances and potential treatment for Philadelphia chromosome-positive adult acute lymphoid leukaemia. *Expert Opin Biol Ther.* Oct 2006;6(10):1011-1022. PMID 16989583
12. Guilhot F, Apperley J, Kim DW, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood.* May 15 2007;109(10):4143-4150. PMID 17264298
13. Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood.* Apr 15 2007;109(8):3207-3213. PMID 17185463
14. Walz C, Sattler M. Novel targeted therapies to overcome imatinib mesylate resistance in chronic myeloid leukemia (CML). *Crit Rev Oncol Hematol.* Feb 2006;57(2):145-164. PMID 16213151
15. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. *Blood.* Aug 16 2012;120(7):1390-1397. PMID 22613793
16. Branford S, Hughes TP, Rudzki Z. Monitoring chronic myeloid leukaemia therapy by real-time quantitative PCR in blood is a reliable alternative to bone marrow cytogenetics. *Br J Haematol.* Dec 1999;107(3):587-599. PMID 10583264
17. Radich JP. Measuring response to BCR-ABL inhibitors in chronic myeloid leukemia. *Cancer.* Jan 15 2012;118(2):300-311. PMID 21717440
18. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med.* Dec 7 2006;355(23):2408-2417. PMID 17151364
19. Press RD, Love Z, Tronnes AA, et al. BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. *Blood.* Jun 1 2006;107(11):4250-4256. PMID 16467199
20. Branford S, Rudzki Z, Harper A, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Leukemia.* Dec 2003;17(12):2401-2409. PMID 14523461
21. Wang L, Pearson K, Ferguson JE, et al. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. *Br J Haematol.* Mar 2003;120(6):990-999. PMID 12648069
22. Quintas-Cardama A, Kantarjian H, Jones D, et al. Delayed achievement of cytogenetic and molecular response is associated with increased risk of progression among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose imatinib therapy. *Blood.* Jun 18 2009;113(25):6315-6321. PMID 19369233
23. Müller MC, Hanfstein B, Erben P, et al. Molecular response to first line imatinib therapy is predictive for long term event free survival in patients with chronic phase chronic myelogenous leukemia – an interim analysis of the randomized German CML Study IV. *Blood* 2008;112:129. Abstract 333. PMID
24. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-alpha in newly diagnosed chronic myeloid leukemia. *J Clin Oncol.* Apr 20 2011;29(12):1634-1642. PMID 21422420
25. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol.* Jul 10 2008;26(20):3358-3363. PMID 18519952
26. Marin D, Milojkovic D, Olavarria E, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood.* Dec 1 2008;112(12):4437-4444. PMID 18716134
27. Baccarani M, Castagnetti F, Gugliotta G, et al. A review of the European LeukemiaNet recommendations for the management of CML. *Ann Hematol.* Apr 2015;94(Suppl 2):S141-147. PMID 25814080
28. Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. *Clin Cancer Res.* Oct 15 2007;13(20):6136-6143. PMID 17947479

29. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. *Blood.* Nov 1 2004;104(9):2926-2932. PMID 15256429
30. Wang L, Knight K, Lucas C, et al. The role of serial BCR-ABL transcript monitoring in predicting the emergence of BCR-ABL kinase mutations in imatinib-treated patients with chronic myeloid leukemia. *Haematologica.* Feb 2006;91(2):235-239. PMID 16461309
31. Press RD, Willis SG, Laudadio J, et al. Determining the rise in BCR-ABL RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. *Blood.* Sep 24 2009;114(13):2598-2605. PMID 19625707
32. Marin D, Khorashad JS, Foroni L, et al. Does a rise in the BCR-ABL1 transcript level identify chronic phase CML patients responding to imatinib who have a high risk of cytogenetic relapse? *Br J Haematol.* May 2009;145(3):373-375. PMID 19344397
33. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *J Clin Oncol.* Aug 1 2009;27(22):3659-3663. PMID 19487383
34. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol.* Dec 10 2009;27(35):6041-6051. PMID 19884523
35. 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.* Aug 4 2011;118(5):1208-1215. PMID 21562040
36. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood.* Jul 1 2006;108(1):28-37. PMID 16522812
37. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med.* Oct 9 2003;349(15):1423-1432. PMID 14534335
38. Cross NC. Standardisation of molecular monitoring for chronic myeloid leukaemia. *Best Pract Res Clin Haematol.* Sep 2009;22(3):355-365. PMID 19959086
39. Hughes T, Branford S. Molecular monitoring of BCR-ABL as a guide to clinical management in chronic myeloid leukaemia. *Blood Rev.* Jan 2006;20(1):29-41. PMID 16426942
40. Terasawa T, Dahabreh I, Castaldi PJ, et al. *Systematic reviews on selected pharmacogenetic tests for cancer treatment: CYP2D6 for Tamoxifen in breast cancer, KRAS for anti-EGFR antibodies in colorectal cancer, and BCR-ABL1 for tyrosine kinase inhibitors in chronic myeloid leukemia.* Rockville, MD: Agency for Healthcare Research and Quality; 2010.
41. Soverini S, De Benedittis C, Polakova KM, et al. Next-generation sequencing for sensitive detection of BCR-ABL1 mutations relevant to tyrosine kinase inhibitor choice in imatinib-resistant patients. *Oncotarget.* Apr 19 2016;7(16):21982-21990. PMID 26980736
42. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? *Blood.* Dec 24 2009;114(27):5426-5435. PMID 19880502
43. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-up of the PACE Trial. *American Society of Hematology 54th Annual Meeting, December 2012.* 2012:Abstract 163. PMID
44. Ernst T, Gruber FX, Pelz-Ackermann O, et al. A co-operative evaluation of different methods of detecting BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia on second-line dasatinib or nilotinib therapy after failure of imatinib. *Haematologica.* Sep 2009;94(9):1227-1235. PMID 19608684
45. Alikian M, Gerrard G, Subramanian PG, et al. BCR-ABL1 kinase domain mutations: methodology and clinical evaluation. *Am J Hematol.* Mar 2012;87(3):298-304. PMID 22231203
46. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program.* 2010;2010:7-12. PMID 21239764

47. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood.* Apr 22 2010;115(16):3206-3214. PMID 20154213
48. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Acute Lymphoblastic Leukemia. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed September 18, 2017.
49. Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. *Leukemia.* Mar 2010;24(3):521-535. PMID 20033054