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Clinical UM Guideline

Subject:	**BCR-ABL Mutation Analysis**		
Guideline #:	**CG-GENE-07**	**Publish Date:**	**05/09/2019**
Status:	**New**	**Last Review Date:**	**03/21/2019**

Description

This document addresses BCR-ABL mutation analysis.

Clinical Indications

Medically Necessary:

BCR-ABL kinase domain point mutation analysis is considered medically necessary in the evaluation of individuals with chronic myelogenous leukemia or BCR-ABL positive acute lymphoblastic leukemia to evaluate treated individuals who manifest suboptimal response to initial tyrosine kinase inhibitor therapy or loss of response to tyrosine kinase inhibitor therapy.

~~Investigational and~~ **Not Medically Necessary:**

All other indications of BCR-ABL mutation analysis are considered ~~investigational and~~ not medically necessary in the management of chronic myelogenous leukemia and acute lymphoblastic leukemia when the above criteria are not met.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage

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or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

~~**When services may be Medically Necessary when criteria are met:**~~

CPT	
81170	***ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)*** **(eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain**
81401	**Molecular pathology procedure, Level 2 (eg, 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) [when specified as the following]:** • ***ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)*** **(eg, acquired imatinib resistance), T315I variant**

ICD-10 Diagnosis	
C91.00-C91.02	Acute lymphoblastic leukemia [ALL]
C92.10-C92.12	Chronic myeloid leukemia, BCR/ABL-positive
C92.20-C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.Z0-C92.Z2	Other myeloid leukemia
C92.90-C92.92	Myeloid leukemia, unspecified

~~**When services are Investigational and Not Medically Necessary:**~~
~~**For the procedure and diagnosis codes listed above when criteria are not met, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.**~~

Note: CPT codes for BCR/ABL translocation analysis are not addressed in this document and are not included.

Discussion/General Information

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Leukemia is a type of cancer that affects the blood and bone marrow. The disease occurs when blood cells produced in the bone marrow grow out of control. There are several types of leukemias. Chronic myelogenous leukemia (CML) is a condition in which the bone marrow makes too many myeloid cells. These blood cells are abnormal and can build up in the blood and bone marrow so there is less room for the healthy white blood cells. CML is a relatively uncommon disease, primarily affecting older adults at an average age of 64 years. Acute lymphoblastic leukemia (ALL) is a disease characterized by the production of immature lymphoid cells in the bone marrow and blood. ALL progresses rapidly without treatment. According to the American Cancer Society (2019), approximately 8990 new cases of CML and approximately 5930 new cases of ALL will be diagnosed in 2019. The risk of developing ALL is highest in children under the age of 5.

Prior to the availability of protein tyrosine kinase inhibitors (TKIs), the only curative option for CML was high-dose chemotherapy with allogeneic stem cell support. Protein TKIs are typically utilized in the treatment of CML. The standard of care for ALL has been hematopoietic stem cell transplantation (HSCT), but with the emergence of BCR-ABL-targeted TKIs, the role of HSCT has become less clear. Several drugs in the protein TKI class have now been approved by the United States Food and Drug Administration for the treatment of CML and ALL. Most individuals have a good response to this first-line of therapy. However, some individuals develop secondary (acquired) resistance to the first-line therapeutic agent, which may be due to secondary mutations of the BCR-ABL gene.

The protein TKIs act to bind the inactive forms of the ABL kinase and function as a competitive inhibitor at the ATP binding site (P-loop) of the BCR-ABL protein. The primary effect is to block the auto-phosphorylation of the kinase, a requirement for kinase activation and signal transduction. The bound BCR-ABL tyrosine kinase is acted upon by phosphatases and remains in an enzymatically inert state. Clinical trials are in progress to research the use of additional medications in conjunction with other treatments such as chemotherapy and stem-cell transplants.

BCR-ABL mutation analysis has been proposed as a diagnostic test to detect secondary mutations in the ABL portion of the BCR-ABL oncogene associated with CML and a cytogenetic subtype of ALL (Philadelphia chromosome positive [Ph+] ALL). There is a commercially available BCR-ABL Mutation test

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(Genzyme Genetics, Westborough, MA) which is designed to detect the presence of BCR-ABL kinase domain mutations. The test is a molecular diagnostic procedure which uses polymerase chain reaction (PCR) amplification and gene sequencing of exons 18-21 of the tyrosine kinase domain of the BCR-ABL fusion gene. The test examines both peripheral blood and bone marrow specimens. Documentation from the manufacturer does not define which specific mutations are included in this test.

CML

The presence of the Philadelphia chromosome (Ph) is what defines CML. Ph occurs when there is a reciprocal translocation between chromosomes 9 and 22 which then gives rise to a BCR-ABL1 fusion gene. Up to 90% of cases of CML have this classical Ph translocation. Unexplained leukocytosis or thrombocytosis may be signs of CML and to assist with the diagnosis and treatment of CML, peripheral blood or bone marrow samples are usually taken for analysis (American Cancer Society, 2019).

Identification of translocations and BCR-ABL mutations as a source of protein TKI resistance may be a useful research tool in understanding the natural history of CML and its transition to more aggressive phenotypes for example, accelerated phase and blast crisis. Although certain BCR-ABL mutations may be associated with protein TKI resistance, the significance of many other mutations is unknown. In addition, the presence of a mutation does not invariably lead to protein TKI resistance (Khorashad, 2006; Willis, 2005).

Primary resistance to protein TKIs is defined as failure to obtain a complete hematologic response, and occurs in roughly 5% of individuals with newly diagnosed CML. While the mechanisms for primary resistance are poorly understood, it is felt to be independent of the BCR-ABL gene. Approximately 20% to 30% of individuals with CML fail to respond to imatinib or have disease relapse after an initial response (Jabbour, 2013). Secondary resistance is defined as loss of a previously established response. Acquired or secondary resistance to protein TKIs may be the result of gene amplification, where increased tyrosine kinase production occurs, or specific point mutations in the BCR-ABL gene. Increasing the dosage of protein TKIs can often overcome the resistance due to gene amplification. Resistance due to BCR-ABL gene mutation is more difficult to treat. BCR-ABL mutations may confer resistance by a variety of mechanisms, but commonly affect conformation of the protein TKI binding site on the tyrosine kinase phosphate binding

loop ("P-loop") or adenosine triphosphate (ATP) binding site such that protein TKI inactivation of tyrosine kinase is blocked. More than 40 different mutations have been associated with resistance to protein TKIs.

Desatinib, a second-generation TKI (ABCR-ABL), has a 325-times higher potency than imatinib against unmutated BCR-ABL *in* vitro (O'Hare, 2005). Since imatinib failure is commonly caused by BCR-ABL mutations, Muller and colleagues (2009) analyzed data from three phase II/III clinical trials which studied the response to desatinib of individuals with chronic phase CML with or without BCR-ABL mutations after prior therapy with imatinib. Of 1043 individuals who underwent mutational assessment, 39% had a BCR-ABL mutation prior to dasatinib and 48% of 805 individuals with either imatinib resistance or a poor response to imatinib had a BCR-ABL gene mutation. A total of 63 different BCR-ABL mutations were detected, with G250, M351, M244, and F359 most frequently found. After 2 years of follow-up, desatinib treatment of imatinib-resistant individuals resulted in a complete cytogenetic response in 43% of individuals with a BCR-ABL mutation and 47% of those without mutation. Progression-free survival was 70% in individuals with BCR-ABL mutation and 80% in those without a mutation. The authors concluded that overall, dasatinib has a durable efficacy in individuals with or without BCR-ABL mutations.

Second-generation TKIs have been approved (desatinib/nilotinib) and shown to be effective against imatinib-resistant CML, with the exception of the BCR-ABL mutant T315-I. Soverini (2007) studied 45 individuals who were resistant or intolerant to imatinib and were treated with the second-generation TKI, dasatinib. With a median follow-up of 12 months, 21 individuals showed either primary or secondary resistance to dasatinib or loss of hematologic response during treatment. Eight individuals had primary resistance to dasatinib, and 13 individuals had secondary resistance to dasatinib. The T315-I mutation accounted for dasatinib treatment failure in 13 of the 21 cases confirming that the T315-I mutation is highly resistant to dasatinib. Additional studies have also confirmed that the mutant T315-I is resistant to TKIs currently available (Branford, 2009; Muller, 2009).

Cortes et al (2012a) reported on a phase I trial of 81 participants with resistant hematologic cancer that had either relapsed, were resistant to standard care or for which no standard care was available or acceptable and received daily ponatinib. Sixty-five of the total participants had CML. At the beginning of the study, 42 of the 65 participants with CML carried at least one BCR-ABL mutation; T315-I was the most frequent

mutation (n=19). All participants received ponatinib daily. Twelve of the participants had chronic-phase CML and a T315-I mutation. Eleven out of 12 had a major cytogenetic response, 9 had a complete cytogenetic response, and 8 had a major molecular response. Of the 7 participants with advanced disease who had the T315-I mutation, 2 had a major hematologic response, 2 had a major cytogenetic response, and 2 had a major molecular response.

Cortes and colleagues (2012b) reported on a phase 2 prospective, single-arm, multicenter, open-label study of 62 participants with chronic-phase CML who harbored the T315-I mutation and who received omacetaxine mepesuccinate. Forty-eight participants achieved complete hematologic response and 14 participants achieved major cytogenetic response. All participants had received prior TKIs and 46 participants had failed therapy with at least two TKIs.

In a 2014 study by Elias and colleagues, 125 individuals with CML who were on imatinib therapy with either TKI refractory or resistance to imatinib were screened for the frequency and pattern of BCR-ABL kinase domain mutations. Mutations were detected in 28 individuals. There were 15 different types of mutations found, including 2 new ones. However, the T315-I mutation was the predominant mutation found. The monitoring of BCR-ABL in individuals with CML ensures that the appropriate selection of individuals for BCR-ABL1 kinase domain mutation analysis associated with acquired TKI resistance.

For individuals with less than a complete response to induction or who 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 multiagent 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 Leukemia Network. 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, 2018).

In a 2018 study by Breccia and colleagues, a total of 29 individuals with CML received ponatinib as second-line therapy following resistance or intolerance to front-line TKI therapy. In this retrospective review, 13 participants received ponatinib for secondary resistance to previous TKI, 11 received ponatinib due to primary resistance to TKI, 2 received ponatinib due to severe intolerance and a molecular warning, 2 received ponatinib due to the presence of the T315I mutation (after imatinib failure), and 1 received ponatinib for severe intolerance to dasatinib. At a median follow-up of 12 months following ponatinib therapy, 2 participants achieved partial cytogenetic response, 2 participants achieved complete cytogenetic response, 11 participants achieved major molecular response, 10 participants achieved a deep molecular response (including 2 participants with T315I) as best response, and 4 participants did not obtain a response. There were no differences in the degree of response in the individuals carrying a mutation at baseline.

ALL
Philadelphia chromosome-positive ALL (Ph+ ALL) is a subtype of ALL. The incidence of Ph+ ALL increases to 20%-40% in adults. 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.

This document addresses gene mutation testing and does not involve gene translocation analysis, such as GenoTRACE® assay.

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Definitions

Apoptosis: A series of molecular steps resulting in a type of cell death. A normal way for the body to get rid of unneeded or abnormal cells. A form of programmed cell death.

First-line of therapy: The first or primary treatment for the diagnosis, may include surgery, chemotherapy, radiation therapy or a combination of these therapies.

Leukemia: A type of cancer that affects the blood and bone marrow.

Leukocytosis: An increase in the number of white blood cells.

Mutation: A permanent transmissible change in DNA sequence. It can be an insertion or deletion of genetic information, or an alteration in the original genetic information.

Oncogene: A gene having the potential to cause a normal cell to become cancerous.

Thrombocytosis: A higher than normal number of platelets.

Translocation: The transfer of part of a chromosome (gene fragment) from one chromosomal location to another.

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13. **Müller MC, Cortes JE, Kim DW, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009; 114(24):4944-4953.**

14. **O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res.2005; 65(11)4500-4505.**
15. **Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica. 2007; 92(3):401-404.**
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Websites for Additional Information

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History

Status	Date	Action
New	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review.
New	03/20/2019	Hematology/Oncology Subcommittee review. Initial document development. Moved content of GENE.00005 BCR-ABL Mutation Analysis to new clinical utilization management guideline with the same title.