

## Corporate Medical Policy

### **BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy**

**File Name:** braf\_gene\_mutation\_testing\_to\_select\_melanoma\_patients\_for\_braf\_inhibitor\_therapy  
**Origination:** 1/2012  
**Last CAP Review:** Not Applicable  
**Next CAP Review:** 3/2012  
**Last Review:** 1/2012

#### **Description of Procedure or Service**

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BRAF inhibitors are drugs designed to target a somatic mutation in the BRAF gene of patients with advanced melanoma. BRAF codes for a kinase component in the the RAF-MEK-ERK signal transduction phosphorylation cascade. The mutated version of the BRAF kinase results in constitutive activity, which is believed to be actively involved in oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to significantly retard tumor growth and may improve patient survival.

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2011, more than 70,000 new cases will be diagnosed. In advanced (Stage 4) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are Stage 4 at diagnosis, prognosis is extremely poor; 5-year survival is about 15-20%.

Dacarbazine has long been considered the treatment standard for systemic therapy, but has disappointingly low response rates of only 15 to 25% and median response durations of 5 to 6 months; less than 5% of responses are complete. Temozolomide has similar efficacy with the exception of a much greater ability ability to penetrate the central nervous system. Combination regimens increase response rates, but not overall survival. Very recently, ipilimumab was approved by the FDA for the treatment of patients with unresectable or metastatic melanoma. For the first time, a survival advantage was demonstrated in previously treated patients: median survival on ipilimumab of 10 months versus 6.4 months on control medication. However, side effects of ipilimumab can include severe and fatal immune-mediated adverse reactions, especially in patients who are already immune-compromised.

Mutations in the BRAF kinase gene are common in tumors of patients with advanced melanoma, and result in constitutive activation of a key signaling pathway that is associated with oncogenic proliferation. In general, 50-70% of melanoma tumors harbor a BRAF mutation and of these, 80% are positive for BRAFV600E. Thus, 40-60% of advanced melanoma patients might respond to a BRAF inhibitor targeted to this mutated kinase.

Two companies developed targeted BRAF inhibitors that have proceeded to phase III clinical trials in melanoma patients. Vemurafenib (trade name Zelboraf®, also known as PLX4032 and RO5185426) was co-developed under an agreement between Roche (Genentech) and Plexxikon. Vemurafenib was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the BRAF V600E mutated kinase, and significantly lower potency to inhibit most of many other kinases tested. Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in BRAF mutant cells and caused regression of BRAF mutant human melanoma xenografts in murine models.

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Paradoxically, preclinical studies also showed that melanoma tumors with the BRAF wild type gene sequence could respond to mutant BRAF-specific inhibitors with accelerated growth, suggesting that it might be harmful to administer BRAF inhibitors to patients with BRAF wild type melanoma tumors. Potentiated growth in BRAF wild type tumors has not yet been confirmed in melanoma patients as the supportive clinical trials were enrichment trials, enrolling only those patients with tumors positive for the BRAFV600E mutation.

Dabrafenib (also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline and is under study in a phase III clinical trial. As few publications detailing preclinical or clinical studies for dabrafenib are available, and neither drug nor companion test (developed by bioMérieux) have as yet been submitted to the FDA, this policy will focus on the the vemurafenib companion test.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## **Policy**

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**BCBSNC will provide coverage for BRAF Gene Mutation Testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## **When BRAF Gene Mutation Testing is covered**

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Testing for the BRAFV600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with vemurafenib.

## **When BRAF Gene Mutation Testing is not covered**

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Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational.

## **Policy Guidelines**

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A large proportion of patients with advanced melanoma have a mutation in the BRAF gene. The Phase III clinical trial of vemurafenib in melanoma patients positive for the BRAFV600E mutation reported a benefit in overall survival and progression-free survival for vemurafenib treatment. These results, which are corroborated by earlier trials, support the clinical validity and clinical utility of the cobas 4800 BRAF V600 Mutation Test, the companion diagnostic test for vemurafenib. Using the test to select patients for treatment results in improved outcomes compared to the usual standard of care, dacarbazine. Thus, this test, and any other tests approved by the FDA to detect the BRAFV600E mutation to select advanced melanoma patients for vemurafenib treatment, may be considered medically necessary.

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## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81210 (Effective 1/1/2012)*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.77, 10/04/11

## **Policy Implementation/Update Information**

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2/7/12 New policy developed. Testing for the BRAFV600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with vemurafenib. Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational. Medical Director review 1/2012. (mco)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.