Medical Policy

**BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy**

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**Policy Number: 398**
BCBSA Reference Number: 2.04.77
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

**Related Policies**
Genetic Testing for Lynch Syndrome and Other Inherited Intestinal Polyposis Syndromes, #226

**Policy**

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**

Testing for BRAFV600 mutations in tumor tissue of patients with unresectable or metastatic melanoma may be **MEDICALLY NECESSARY** to select patients for treatment with FDA-approved BRAF inhibitors.

Testing for BRAFV600 mutations for all other patients with melanoma, including but not limited to use in patients with resectable melanoma, is **INVESTIGATIONAL**.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

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

[Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)](https://www.cms.gov)

For medical necessity criteria and coding guidance for Medicare 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](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

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Prior Authorization Requirement</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is not required.</td>
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</table>

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, and Indemnity:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81210</td>
<td>BRAF Raf proto-oncogene, serine/threonine kinase (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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Description

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2013, there were more than 76,000 new cases.1 In advanced (stage IV) 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% to 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.2 Temozolomide has similar efficacy with the exception of a much greater ability to penetrate the central nervous system.

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 (RAF-MEK-ERK [also called MAPK] pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a BRAF mutation; of these, 80% are positive for BRAF V600E and 16% are positive for BRAF V600K.3 Thus, approximately 45% to 60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase.

Three BRAF inhibitors have been developed for use in patients with advanced melanoma. Vemurafenib (trade name Zelboraf®, also known as PLX4032 and RO5185426) was codeveloped 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 with significantly lower potency to inhibit most of many other kinases tested.4 Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in BRAF mutant cells5-7 and caused regression of BRAF mutant human melanoma xenografts in murine models.4 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,5-7 suggesting that it may 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 patients with tumors positive for the BRAF V600E mutation.
Dabrafenib (Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline (GSK).\textsuperscript{8,9} Dabrafenib inhibits several kinases, including mutated forms of BRAF kinase, with greatest activity against V600E-mutated BRAF. In vitro and in vivo studies demonstrated dabrafenib’s ability to inhibit growth of BRAF V600-mutated melanoma cells.\textsuperscript{10}

Trametinib (Mekinist™) is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 developed by GSK. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. BRAF V600E and V600K mutations result in constitutive activation of MEK1 and MEK2.\textsuperscript{11} Trametinib inhibits growth of BRAF V600 mutation-positive melanoma cells in vitro and in vivo.\textsuperscript{12}

Nivolumab (Opdivo®, also known as BMS-936558, MDX-1106, or ONO-4538) is a genetically engineered, fully human immunoglobulin G4 monoclonal anti-programmed death-1 protein antibody developed by Ono Pharmaceutical and Medarex and manufactured by Bristol-Myers Squibb.

**Summary**

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

The evidence for BRAF gene mutation testing and treatment with Food and Drug Administration–approved BRAF inhibitors when results are positive in select patients who have unresectable or metastatic melanoma includes studies of analytic validity and randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies of analytic validity show that BRAF mutation testing kits have high concordance with the reference standard of Sanger sequencing. Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of BRAF mutation testing have shown improvements in overall survival and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments shows superior outcomes for most end points.

Combination BRAF inhibitor treatment with dabrafenib plus trametinib shows superior overall survival when compared with either vemurafenib or dabrafenib alone. Data showing treatment effects in patients without BRAF mutations do not exist; therefore BRAF mutation testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>6/2016</td>
<td>BCBSA National medical policy review. Information about additional FDA-approved BRAF inhibitor (nivolumab) added to policy. 6/1/2016</td>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
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<tr>
<td>11/2015</td>
<td>Clarified coding information.</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
</tr>
<tr>
<td>12/2014</td>
<td>BCBSA National medical policy review. Policy statements clarified to align with current FDA-approved indication, ie, “unresectable or metastatic” rather than “stage IIIIC or IV.” Effective 12/1/2014.</td>
</tr>
<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>11/2013</td>
<td>New references from BCBSA National medical policy.</td>
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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


