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)

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.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
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**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:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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. 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. 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.

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. 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. 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 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 \textit{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 \textit{BRAF}. In vitro and in vivo studies demonstrated dabrafenib’s ability to inhibit growth of \textit{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. \textit{BRAF} V600E and V600K mutations result in constitutive activation of MEK1 and MEK2.\textsuperscript{11} Trametinib inhibits growth of \textit{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.

\textbf{Summary}

\textit{BRAF} inhibitors are drugs designed to target a somatic mutation in the \textit{BRAF} gene of patients with advanced melanoma. \textit{BRAF} encodes a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. Mutated \textit{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 \textit{BRAF} gene mutation testing and treatment with Food and Drug Administration–approved \textit{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 \textit{BRAF} mutation testing kits have high concordance with the reference standard of Sanger sequencing. Randomized phase 3 trials of \textit{BRAF} inhibitor therapy in patients selected on the basis of \textit{BRAF} mutation testing have shown improvements in overall survival and progression-free survival. Single-agent \textit{BRAF} inhibitor treatment compared with nontargeted treatments shows superior outcomes for most end points.

Combination \textit{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 \textit{BRAF} mutations do not exist; therefore \textit{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.

\textbf{Policy History}

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<th>Date</th>
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<tr>
<td>6/2016</td>
<td>BCBSA National medical policy review. Information about additional FDA-approved \textit{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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<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>
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<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 IIIC or IV,” Effective 12/1/2014.</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</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
14. FDA. In vitro companion diagnostic devices: guidance for industry and food and drug administration staff, 08/06/2014.
17. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Special Report. Companion 
diagnostics: Example of BRAF testing to select patients with melanoma for BRAF kinase inhibitors. 
TEC Assessment Program. 2011;26(7).
18. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and 
14. PMID 18813139
mutations in the BRAF gene, used as the companion diagnostic test for the novel BRAF inhibitor 
Polymerase Chain Reaction Assay for the Detection of BRAF V600E Mutations in Formalin-Fixed, 
Paraffin-Embedded Tissue Specimens of Malignant Melanoma. Arch Pathol Lab Med. 2012/11/01 
2012;136(11):1385-1391. PMID
25. FDA. THxID™-BRAF kit for use on the ABI 7500 Fast Dx Real-Time PCR Instrument - P120014. 
August 13, 2015.
PMID 22735384
for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. 
31. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology, 