Regence

Medical Policy Manual Genetic Testing, Policy No. 41

BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Effective: November 1, 2024

Next Review: July 2025
Last Review: September 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

BRAF and MEK inhibitors are drugs that were originally designed to target a variant in the *BRAF* gene found in some advanced melanoma tumors. This BRAF-variant kinase is believed to be actively involved in oncogenic proliferation, and specific inhibition of the kinase has been shown to slow tumor growth and may improve patient survival.

MEDICAL POLICY CRITERIA

I. Testing for *BRAF* variants in tumor tissue to select targeted therapy may be considered **medically necessary** for patients with advanced, metastatic, or unresectable melanoma.

II. Testing for *BRAF* variants for all other patients with melanoma is considered **investigational**.

III. Testing for *BRAF* variants in tumor tissue to select targeted therapy may be considered **medically necessary** for patients with glioma.

IV. Testing for *BRAF* variants for patients with glioma is considered **investigational** for all other purposes.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes, Genetic Testing, Policy No. 06
2. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83

BACKGROUND

MELANOMA

Overall incidence rates for melanoma have been increasing for at least 30 years. 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 IV at diagnosis, prognosis is poor, with a five-year survival of only 15-20%. For several decades since its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has low response rates of only 15-25% and median response durations of five to six months. Less than 5% of responses are complete.[1] Temozolomide has similar efficacy with a greater ability to penetrate the central nervous system. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy[2-6] regardless of *BRAF* status and is now recommended as one potential first-line treatment of metastatic or unresectable melanoma by the National Comprehensive Cancer Network (NCCN).[7]

Variants 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 to 70% of melanoma tumors harbor a *BRAF* variant and of these, 80% are positive for *BRAF* V600E and 16% are positive for *BRAF* V600K.[8] Thus,

approximately 45% to 60% of advanced melanoma patients might respond to a BRAF inhibitor targeted to this variant kinase.

BRAF inhibitors (e.g., vemurafenib, dabrafenib) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (e.g., trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. 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 variant kinase and significantly lower potency to inhibit most of many other kinases tested.[9] Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in *BRAF*-variant cells[10-12] and caused regression of *BRAF*-variant human melanoma xenografts in murine models.[9] Paradoxically, preclinical studies also showed that melanoma tumors with the *BRAF* wild-type gene sequence could respond to variant BRAF-specific inhibitors with accelerated growth,[10-12] 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 *BRAF* V600E variant.

Dabrafenib (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline, now Novartis.[13, 14] Dabrafenib inhibits several kinases, including variant forms of BRAF, with greatest activity against the V600E BRAF variant. In vitro and in vivo studies demonstrated dabrafenib's ability to inhibit growth of *BRAF* V600 variant-positive melanoma cells.[15]

Trametinib (trade name Mekinist™) is an inhibitor of MEK1 and MEK2 developed by GlaxoSmithKline. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2.[16] Trametinib inhibits growth of BRAF V600 variant-positive melanoma cells in vitro and in vivo.[17]

Cobimetinib, formally GDC-0973/XL518 (trade name Cotellic®) was developed by Genentech[18] and Exelixis[19]. It is a MEK inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.

Nivolumab (OPDIVO®), developed by Bristol-Myers Squibb, is not a BRAF or MEK inhibitor, but instead inhibits the PD-1 protein on cells. PD-1 blocks the body's immune system from attacking melanoma tumors. Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express a *BRAF* V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor.

GLIOMA

Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, World Health Organization (WHO) published an update of its classification of gliomas based on both histopathologic appearance and molecular parameters.[20] The classification ranges from grade I to IV corresponding to the degree of

malignancy (aggressiveness) with WHO grade I being least aggressive and grade IV being most aggressive.

Low-grade gliomas were historically those classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, along with additional radiation and chemotherapy following surgery except in the case of pilocytic astrocytoma. The optimal timing of additional therapies is unclear. Many patients will recur following initial treatment with a clinical course similar to high-grade glioma. High-grade gliomas (WHO grade III/IV) include anaplastic gliomas and glioblastoma. Maximal surgical resection is the initial treatment followed by combined adjuvant chemoradiotherapy. Temozolomide, an oral alkylating agent, is considered standard systemic chemotherapy for malignant gliomas. The prognosis for patients with high-grade gliomas is poor: the one-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.[21]

There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, *BRAF* V600E variants have been found in approximately 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma.[22-27] However, it may be rare in adult glioblastoma.[28] There is considerable interest in targeted therapies that inhibit the MAPK pathway, particularly in patients with high-grade glioma and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early phase trials in patients with *BRAF* variant-positive melanoma with brain metastases suggest some efficacy for brain tumor response with vemurafenib and dabrafenib,[29, 30] indicating that these agents might be potential therapies for primary brain tumors.

REGULATORY STATUS

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, released on July 14, 2011,[31] to address the "emergence of new technologies that can distinguish subsets of populations that respond differently to treatment." As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices "when an appropriate scientific rationale supports such an approach." In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

- **Vemurafenib**

  Vemurafenib and a Class III companion diagnostic test, the cobas® 4800 BRAF V600 Mutation Test, were co-approved by the FDA in August 2011.[32] The test is approved as an aid in selecting melanoma patients whose tumors carry the *BRAF* V600 variant for treatment with vemurafenib.[33] Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 variant. The vemurafenib full prescribing information states that confirmation of a *BRAF* V600 variant using an FDA-approved test is required for selection of patients appropriate for therapy.[34]

- **Dabrafenib**

Dabrafenib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variant, as detected by an FDA-approved test.[15] A 2018 updated approval indicates that it may be used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Dabrafenib is specifically not indicated for the treatment of patients with wild-type *BRAF* melanoma.

- **Trametinib**

Trametinib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants, as detected by an FDA-approved test.[17] A 2018 update indicates that it may be used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy.[17]

- **Nivolumab**

Nivolumab was originally FDA-approved December 2014 for the treatment of unresectable or metastatic melanoma.[35] Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express an activating BRAF V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor. Nivolumab may also be used in combination with ipilimumab in patients without a *BRAF* V600 variant.

- **Cobimetinib**

Cobimetinib was FDA-approved November 2015 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib, as detected by an FDA-approved test. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.[36]

- **Binimetinib**

Binimetinib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with encorafenib.

- **Encorafenib**

Encorafenib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with binimetinib.

In 2014, the FDA granted accelerated approval of trametinib and dabrafenib as a combination therapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test.[37] Approval of the combination therapy was based on the demonstration of durable objective responses in a multicenter, open-label, randomized (1:1:1), active-controlled, dose-ranging trial enrolling 162 patients with histologically confirmed Stage IIIC or IV melanoma determined to be *BRAF* V600E or V600K. No more than one prior chemotherapy regimen and/or interleukin-2 were permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

In November 2015, cobimetinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variant, in combination with vemurafenib.[36] Additionally, in 2011, ipilimumab (Yervoy®) 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. Ipilimumab's clinical study did not test metastatic melanoma patients' tumors for *BRAF* status; therefore, it's not known what, if any, clinical relevance *BRAF* status has with respect to ipilimumab.

In 2018, the FDA approved encorafenib and binimetinib together for unresectable or metastatic melanoma with *BRAF* V600 variants.

In 2022, the FDA approved dabrafenib and trametinib together for unresectable or metastatic solid tumors with *BRAF* V600 variants.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on the clinical validity and utility of testing.

BRAF TESTING TO SELECT TREATMENT FOR MELANOMA

For individuals with melanoma who receive *BRAF* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

GLIOMA

For individuals with glioma who receive *BRAF* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

NCCN guidelines for cutaneous melanoma (v.2.2024) includes the following recommendations:[7]

- The panel does not recommend *BRAF* or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation.
- *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future *BRAF*-directed therapy may be an option.
- For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g., larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.
- If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT*, *BRAF* non-V600).

The NCCN guidelines for central nervous system cancers (v.2.2024) state the following:[38]

- The panel encourages molecular testing of glioblastoma because if a driver mutation (such as *BRAF* V600E or *NTRK* fusion) is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial.
- Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.

The NCCN guidelines for pediatric central nervous system cancers (v.1.2024) include a recommendation to test for *BRAF* V600E and *BRAF* fusion for pediatric gliomas, and further recommend that preferred systemic therapy options for recurrent disease include, but are not limited to, dabrafenib/trametinib or vemurafenib for *BRAF* V600E-positive tumors.[39]

SUMMARY

There is enough research to show that *BRAF* variant testing can improve health outcomes for some melanoma patients by helping them to select an FDA-approved targeted treatment. In addition, clinical practice guidelines recommend treatment with these BRAF inhibitors in certain patients with a V600 *BRAF* variant. Therefore, *BRAF* variant testing may be considered medically necessary to select treatment for patients with advanced, metastatic, or unresectable melanoma. Testing for *BRAF* variants for all other patients with melanoma is considered investigational, as there are no FDA-approved *BRAF*-targeted therapies for early-stage melanoma.

There is enough research to show that *BRAF* variant testing can improve health outcomes for some glioma patients by helping them to select an FDA-approved targeted treatment. In addition, clinical practice guidelines recommend treatment with these BRAF inhibitors in certain patients with a V600 *BRAF* variant. Therefore, *BRAF* variant testing may be considered medically necessary to select treatment for patients with glioma. Testing for *BRAF* variants for other purposes is considered not medically necessary.

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CODES

Codes	Number	Description
CPT	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
HCPCS	None	

Date of Origin: *January 2012*