BlueCross BlueShield of Alabama

Name of Policy:

BRAF Gene ~~Mutation~~ Variant Testing To Select Melanoma or Glioma Patients for Targeted Therapy

Policy #: 541
Category: Laboratory

Latest Review Date: July 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

BRAF and *MEK* inhibitors are drugs designed to target a somatic variant in the *BRAF* gene. The inhibitors were originally developed for 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 retard tumor growth significantly and may improve patient survival.

Melanoma

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2017, there were more than 87,100 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 IV at diagnosis, prognosis is extremely poor; five-year survival is about 15-20%.

Treatment

Unresectable or Metastatic Melanoma

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has provided disappointingly low response rates of only 15% to 25% and median response duration of 5 to 6 months; less than 5% of responses are complete. Temozolomide has similar efficacy and, unlike dacarbazine, has much better efficacy with central nervous system tumors. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy regardless of *BRAF* status and is now recommended as a potential first-line treatment of metastatic or unresectable melanoma.

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

Two *BRAF* inhibitors (vemurafenib, dabrafenib) and 2 MEK inhibitors (trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (also known as PLX4032 and RO5185426) 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 have 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, because the supportive clinical trials were enrichment trials, enrolling only patients with tumors positive for the *BRAF* V600E variant.

Dabrafenib (also known as GSK2118436 or SB-590885) 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.

Trametinib is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK kinases regulate the extracellular signal-related kinase, which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2. Trametinib inhibits the growth of *BRAF* V600 variant–positive melanoma cells in vitro and in vivo.

Cobimetinib is a MEK1 and MEK2 inhibitor. Co-administration of cobimetinib and vemurafenib has resulted in increased apoptosis and reduced tumor growth of *BRAF* V600E tumor cells in vitro, and cobimetinib has prevented the vemurafenib-mediated growth of a wild-type *BRAF* tumor cells in vivo.

Resected Stage III Melanoma
Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer Stage III melanoma may receive adjuvant therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients who had resected Stage III disease. Nivolumab, a programmed cell death protein 1 blocking antibody, has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months. Before the development of checkpoint inhibitor immunotherapy and targeted therapy, high-dose interferon alfa was an option for adjuvant treatment of Stage III melanoma. Interferon alfa has demonstrated an improvement in overall survival but with numerous serious side effects.

Glioma
More than 79,000 new cases of primary malignant and nonmalignant brain and other central nervous system tumors are expected to be diagnosed in the United States in 2017, the majority of which are gliomas. Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, the World Health Organization (WHO) updated its classification of gliomas based on both histopathologic appearance and molecular parameters. 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.

<u>Treatment</u>
Low-grade gliomas are classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, although additional therapy with radiotherapy and chemotherapy following surgery is usually required, except for 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 1-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.

There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, *BRAF* V600E variants have been found in 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma. However, it may be rare in adult glioblastoma.

There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade 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 has suggested some efficacy for brain tumor response with vemurafenib and dabrafenib, indicating that these agents might be potential therapies for primary brain tumors.

Policy:

Effective for dates of service on or after August 1, 2018:

Testing for *BRAF*V600 variants in tumor tissue of patients with **unresectable or metastatic melanoma** to select patients for treatment with FDA-approved BRAF or MEK inhibitors **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Testing for *BRAF* V600 variants in tumor tissue of patients with **resected Stage III melanoma** to select patients for treatment with FDA–approved *BRAF* or MEK inhibitors **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Testing for *BRAF*V600 variants for **all other patients with melanoma**, ~~including but not limited to, use in patients with resectable melanoma~~, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Testing for BRAFV600 variants for patients with **glioma** to select patients for targeted treatment does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered investigational.

~~***Note:** Vemurafenib, dabrafenib, trametinib, and cobimetinib are currently approved by the U.S. Food and Drug Administration (FDA) specifically to treat advanced *BRAF* variant melanoma. There are no FDA-approved targeted therapies for *BRAF* V600 variant positive glioma~~.

Effective for dates of service September 19, 2017 through July 31, 2018:
Testing for *BRAF*V600 variants in tumor tissue of patients with **unresectable or metastatic melanoma** to select patients for treatment with FDA-approved BRAF or MEK inhibitors **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Testing for *BRAF* V600 variants in tumor tissue of patients with resected Stage III melanoma to select patients for treatment with FDA–approved *BRAF* or MEK inhibitors **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Testing for *BRAF*V600 variants for **all other patients with melanoma**, including but not limited to, use in patients with resectable melanoma, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Testing for BRAFV600 variants for patients with glioma to select patients for targeted treatment does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

***Note:** Vemurafenib, dabrafenib, trametinib, and cobimetinib are currently approved by the U.S. Food and Drug Administration (FDA) specifically to treat advanced *BRAF*-variant melanoma. There are no FDA-approved targeted therapies for *BRAF* V600 variant–positive glioma.

Effective for dates of service prior to September 19, 2017:
Testing for *BRAF*^{V600} mutations in tumor tissue of patients with unresectable or metastatic melanoma **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage to select patients for treatment with FDA-approved *BRAF* inhibitors.

Testing for *BRAF*^{V600} mutations for all other patients with melanoma, including but not limited to, use in patients with resectable melanoma, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature update was performed through April 9, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Unresectable or Metastatic Melanoma

When treatment is developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is co-developed to identify diseased patients with that target, clinical validity and clinical utility cannot be evaluated separately. Rather, clinical studies of treatment benefit, which use the test to select patients, provide evidence of both clinical validity and clinical utility. We reviewed the Phase 3 clinical trials of treatments in which testing for the *BRAF* variant was required for selection into the trial. In the absence of clinical trials in which *both* patients with and without *BRAF* variants are entered into RCTs of novel therapies, we cannot be certain that the test has clinical utility because it is unknown whether the treatment would be effective in patients without *BRAF* variant. However, patients without *BRAF* variants have not been enrolled in clinical trials of *BRAF* inhibitors.

Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with unresectable or metastatic melanoma is to inform a decision whether to treat with *BRAF* or MEK tyrosine kinase inhibitors or with other standard treatments for metastatic melanoma. At the time of the early trials of targeted therapy for metastatic melanoma, cytotoxic chemotherapy (e,g,, dacarbazine, temozolomide) was widely used to treat metastatic melanoma and was therefore considered a comparator, although it was never demonstrated to improve survival. Chemotherapy is now generally used only in second- or third-line settings or not at all. The current standard treatment for patients with metastatic melanoma includes immunotherapy, which is effective in patients with and without *BRAF* V600 variants. Patients whose tumors contain a *BRAF* V600 pathogenic variant may receive a *BRAF* inhibitor and/or a MEK inhibitor instead of or following immunotherapy. There are no randomized controlled trials (RCTs) directly comparing BRAF and MEK inhibitors with immunotherapy, and no prospective data on optimal sequencing of BRAF and MEK inhibitors and immunotherapy for patients with a *BRAF* V600 pathogenic variant.

The question addressed in this evidence review is: Does testing for *BRAF* V600 pathogenic variants to select treatment improve the net health outcome in individuals with unresectable or metastatic melanoma?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with Stage IIIC or stage IV unresectable or metastatic melanoma.

Interventions
The cobas 4800 *BRAF* V600 test and THxID *BRAF* kit are companion diagnostics approved by the U.S. Food and Drug Administration (FDA) for selecting patients for treatment with FDA-approved *BRAF* or MEK inhibitors.

Comparators
The comparator of interest is the standard treatment for metastatic melanoma without genetic testing for *BRAF* variants.

Outcomes
The primary outcomes of interest are overall survival (OS) and progression-free survival (PFS). False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, which have not been shown to be effective in patients without *BRAF* V600 pathogenic variants, and also could lead to delay in treatment with immunotherapy.

Timing
Due to the poor prognosis of metastatic melanoma, demonstration of improvement in survival outcomes at 6 months and 1 year are important.

Setting
Patients suspected of having melanoma should be urgently referred for management by specialists. A multidisciplinary group of specialists involved in caring for patients with metastatic melanoma includes dermatologists, oncologists, and plastic surgeons.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid and Clinical Usefulness
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Vemurafenib

The primary evidence of clinical validity and utility for the cobas 4800 *BRAF* V600 Mutation Test is provided by the Phase 3 clinical trial of vemurafenib that enrolled patients testing positive for a V600 variant.

The BRIM-3 Trial as reported by Chapman et al (2011) is summarized in Table 1. A total of 675 patients were randomized to vemurafenib (960 mg twice daily orally) or to dacarbazine (1000 mg/m^2 body surface area by intravenous infusion every 3 weeks) to determine whether vemurafenib would prolong the rate of OS or PFS compared with dacarbazine. All enrolled patients had unresectable, previously untreated Stage IIIC or IV melanoma with no active central nervous system metastases. Melanoma specimens from all patients tested positive for the *BRAF* V600E variant on the cobas 4800 *BRAF* V600 Mutation Test. Included were 19 patients with *BRAF* V600K variants and 1 with a *BRAF* V600D variant.

Tumor assessments, including computed tomography, were performed at baseline, at weeks 6 and 12, and every 9 weeks after that. Tumor responses were determined by investigators using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Primary end points were the rate of OS and PFS. An interim analysis was planned at 98 deaths and a final analysis at 196 deaths; the published report is the interim analysis. The data and safety monitoring board determined that both coprimary end points had met prespecified stopping criteria and recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib. At the time the trial was halted, 118 patients had died; median survival had not been reached. Results for OS strongly favored vemurafenib, with a hazard ratio (HR) of 0.37 (95% confidence interval [CI], 0.26 to 0.55). Adverse events in the vemurafenib group included grade 2 or 3 photosensitivity skin reactions in 12% of patients and cutaneous squamous cell carcinoma in 18%. The results of this trial comprised the efficacy and safety data supporting vemurafenib submission to FDA and established safety and effectiveness of the cobas 4800 *BRAF* V600 Mutation Test, resulting in co-approval of both the drug and companion test.

Final OS results from BRIM-3 were reported by Chapman et al (2017). Eighty-four (25%) of the 338 dacarbazine patients crossed over to vemurafenib and overall 173 (51%) of the 338 patients in the dacarbazine group and 175 of the 337 patients (52%) in the vemurafenib group received subsequent anticancer therapies, most commonly ipilimumab. Median OS without censoring at crossover was 13.6 months (95% CI, 12.0 to 15.4) in vemurafenib vs 10.3 months (95% CI, 9.1 to 12.8 months) in dacarbazine (HR=0.81; 95% CI, 0.68 to 0.96); p=0.01).

Table 1. Phase 3 RCTs of *BRAF* and MEK Inhibitors for *BRAF*-Positive Advanced Melanoma

Study/Year	FU, mo	Group	N	OS (95% CI)	PFS (95% CI), mo	ORR (95% CI)
Vemurafenib						
Chapman et al (2011)	6	Vemurafenib	337	84% (78% to 89%)	5.3[a]	48% (42% to 55%)
		Dacarbazine	338	65% (56% to 73%)	1.6[a]	5% (3% to 9%)
		Hazard ratio		0.37 (0.26 to 0.55)	0.26 (0.20 to 0.33)	NA
		p		<0.001	<0.001	NA
Dabrafenib						
Hauschild et al (2012)	4.9[a] 0-9.9[b]	Dabrafenib	187	89%	5.1[a]	50% (42.4% to 57.1%)

Study/Year	FU, mo	Group	N	OS (95% CI)	PFS (95% CI), mo	ORR (95% CI)
		Dacarbazine	63	86%	2.7[a]	6% (1.8% to 15.5%)
		Hazard ratio		0.61 (0.25 to 1.48)	0.33 (0.20 to 0.54)	NA
		p		NR	<0.001	NA
Trametinib						
Flaherty et al (2012)	6	Trametinib	214	81%	4.8 (4.3 to 4.9)[a]	22% (17% to 28%)
		Chemotherapy	108	67%	1.5 (1.4 to 2.7)[a]	8% (4% to 15%)
		Hazard ratio		0.54 (0.32 to 0.92)	0.47 (0.34 to 0.65)	NA
		p		0.01	<0.001	NA
Dabrafenib plus trametinib						
Long et al (2015)		Dabrafenib plus trametinib	211	74%	11.0	NA
		Dabrafenib	212	68%	8.8	NA
		Hazard ratio		0.71 (0.55 to 0.92)	0.67 (0.53 to 0.84)	NA
		p		0.01	<0.001	NA
Robert et al (2015)	NR	Dabrafenib plus trametinib	352	72%	11.4	64%
		Vemurafenib	352	65%	7.3	51%
		Hazard ratio		0.69 (0.53 to 0.89)	0.56 (0.46 to 0.69)	NA
		p		0.005	0.001	0.001
Vemurafenib plus cobimetinib						
Ascierto et al (2016)	14[a]	Vemurafenib plus cobimetinib	248	22.3% (20.3% to NE)	12.3 (9.5 to 13.4)	68% (61% to 73%)
		Vemurafenib	247	17.4% (15.0% to 19.8%)	7.2 (5.6 to 7.5)	45% (38% to 51%)
		Hazard ratio		0.70 (0.55 to 0.90)	0.58 (0.46 to 0.72)	NA
		p		0.005	<0.001	<0.001
Encorafenib plus binimetinib						
Dummer et al (2018)	17[a]	Encorafenib plus binimetinib	192	NR	14.9 (11.0 to 18.5)	63% (56% to 70%)
		Encorafenib	194	NR	9.6 (7.5 to 14.8)	51% (43% to 58%)
		Vemurafenib	191		7.3 (5.6 to 8.2)	40% (33% to 48%)
		Hazard ratio[d]			0.54 (0.41 to 0.71)	NR
		p			<0.001	

CI: confidence interval; FU: follow-up; NA: not applicable; NE: not estimable; NR: not reported; ORR: objective response rate (including complete and partial responses); OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial.

[a] Median value.

[b] Range.

[c] Either intravenous dacarbazine 1000 mg/m^2 or intravenous paclitaxel 175 mg/m^2 every 3 weeks at investigator discretion.

[d] Compared encorafenib plus binimetinib with vemurafenib.

Dabrafenib

One Phase 3, open-label RCT of dabrafenib for advanced (Stage IV or unresectable Stage III) melanoma has been published; the results of this trial are summarized in Table 1. The main objective of this RCT was to compare the efficacy of dabrafenib with standard dacarbazine treatment in patients who had *BRAF* V600E–variant metastatic melanoma. Two hundred fifty patients were randomized 3:1 to oral dabrafenib 150 mg twice daily or to intravenous dacarbazine 1000 mg/m^2 every 3 weeks. The primary outcome was PFS, and secondary outcomes were OS, objective response rate, and adverse events.

Median PFS for the dabrafenib and dacarbazine groups was 5.1 months and 2.7 months ($p<0.001$), respectively. OS did not differ significantly between groups: 11% of patients in the dabrafenib group died compared with 14% in the dacarbazine group (HR=0.61; 95% CI, 0.25 to 1.48). However, 28 (44%) patients in the dacarbazine arm crossed over at disease progression to receive dabrafenib. The objective response rate, defined as complete plus partial responses, was higher in the dabrafenib group (50%; 95% CI, 42.4% to 57.1%) than in the dacarbazine group (6%; 95% CI, 1.8% to 15.5%). Treatment-related adverse events of Grade 2 or higher occurred in 53% of patients who received dabrafenib and in 44% of patients who received dacarbazine. Grade 3 and 4 adverse events were uncommon in both groups. The most common serious adverse events were cutaneous squamous cell carcinoma (7% vs none in controls); serious noninfectious, febrile drug reactions (3% grade 3 pyrexia vs none in controls); and severe hyperglycemia (>250-500 mg/dL) requiring medical management in nondiabetic patients or change in management of diabetic patients (6% vs none in controls).

Trametinib

The clinical efficacy and safety of trametinib was assessed in the Phase III, open-label METRIC Trial. Patients with Stage IV or unresectable Stage IIIC cutaneous melanoma were randomized 2:1 to trametinib 2mg orally once daily (n=214) or to chemotherapy (n=108), either dacarbazine 1,000 mg/m² IV every three weeks or paclitaxel 175 mg/m² IV every three weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy end point was PFS; secondary end points included overall survival, overall response rate, and safety. Tumor assessments were performed at baseline and weeks 6, 12, 21, and 30 and then every 12 weeks.

Median PFS was 4.8 months (95% CI, 4.3 to 4.9 months) in the trametinib arm and 1.5 months (95% CI, 1.4 to 2.7 months) in the chemotherapy arm ($p<0.001$) (see Table 1). Although median OS had not been reached at the time of the report publication, 6-month survival was statistically longer in the trametinib group than in the chemotherapy group ($p=0.01$); 51 (47%) of 108 patients in the chemotherapy group had crossed over at disease progression to receive trametinib. Decreased ejection fraction or ventricular dysfunction was observed in 14 (7%) patients in the trametinib group; 2 patients had grade 3 cardiac events that led to permanent drug discontinuation. Twelve percent of the trametinib group and 3% of the chemotherapy grouped experienced grade 3 hypertension. Nine percent of patients in the trametinib group experienced ocular events (mostly grade 1 or 2), most commonly blurred vision (4%). The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, and fatigue; rash was grade 3 or 4 in 16 (8%) patients. Cutaneous squamous cell carcinoma was not observed during treatment.

Combination BRAF Plus MEK Inhibitors

Dabrafenib and Trametinib

The efficacy of combination dabrafenib plus trametinib treatment has been established with two Phase 3 clinical trials. This combination agent was evaluated in the Phase 3 open-label trial by Long et al (2014, 2015). In this trial, 4234 patients with unresectable Stage IIC or Stage IV melanoma with a *BRAF* V600E or V600K variant were randomized to dabrafenib plus trametinib or dabrafenib plus placebo. The primary end point was PFS, as reported in a first publication, followed by a second publication in which longer term OS was reported.

Median PFS was 11.0 months in the dabrafenib plus trametinib group and 8.8 months in the dabrafenib-only group. The overall response rate was 67% in the dabrafenib plus trametinib group and 51% in the dabrafenib-only group. An interim OS analysis showed a statistically significant difference using standard statistical criteria, but the difference did not cross the prespecified stopping boundary. The rate of cutaneous squamous cell carcinoma was lower in the dabrafenib plus trametinib group (2% vs 9%), whereas pyrexia occurred in more patients (51% vs 28%). In the longer term study assessing OS, median survival was 25.1 months in the dabrafenib plus trametinib group and 18.7 months in the dabrafenib-only group.

Another Phase 3 RCT, by Roberts et al (2015), compared dabrafenib plus trametinib with vemurafenib. A total of 704 patients with metastatic melanoma with *BRAF* V600E or V600K variants were randomized equally. The trial was terminated at a preplanned interim OS analysis. The OS rate at 12 months was 72% for dabrafenib plus trametinib and 65% for vemurafenib ($p=0.005$) (see Table 1). Median PFS was 11.4 months for dabrafenib plus trametinib and 7.3 months for vemurafenib ($p<0.001$). The objective response rate was 64% for dabrafenib plus trametinib and 51% for vemurafenib ($p<0.001$). Rates of severe adverse events were similar in both groups. Cutaneous squamous cell carcinoma and keratoacanthoma occurred in 1% of dabrafenib plus trametinib subjects and 18% of vemurafenib subjects.

Vemurafenib Plus Cobimetinib

A multicenter, randomized, double-blinded, placebo-controlled Phase 3 trial evaluated vemurafenib plus cobimetinib in 495 patients with previously untreated, *BRAF* V600 variant–positive, unresectable or metastatic melanoma. All patients received vemurafenib 960 mg orally twice daily on days 1 to 28 and were randomized 1:1 to also receive cobimetinib 60 mg once daily on days 1 to 21 or to placebo. The primary outcome was PFS. Analyses were done on the intention-to-treat population. Median follow-up was 14 months (see Table 1). PFS was significantly increased with vemurafenib plus cobimetinib compared with vemurafenib plus placebo (median PFS, 12.3 months vs 7.2 months; HR=0.58; 95% CI, 0.46 to 0.72; $p<0.001$). Median OS was 22 months for vemurafenib plus cobimetinib and 17 months for vemurafenib plus placebo (HR=0.70; 95% CI, 0.55 to 0.90; $p=0.005$). Serious adverse events were reported in 92 (37%) patients in the vemurafenib plus cobimetinib group and 69 (28%) patients in the vemurafenib plus placebo group. The most common serious adverse events in the vemurafenib plus cobimetinib group were pyrexia and dehydration. The most common grade 3 or 4 adverse events occurring in the vemurafenib plus cobimetinib group were γ-glutamyl transferase increase, blood creatine phosphokinase increase, and alanine transaminase.

Encorafenib Plus Binimetinib

Dummer et al (2018) reported on results of a Phase 3 COLUMBUS RCT comparing encorafenib, a *BRAF* inhibitor, alone or in combination with the MEK inhibitor binimetinib, with vemurafenib in patients who had advanced *BRAF* V600–variant unresectable or metastatic melanoma. The COLUMBUS Trial was conducted in 162 hospitals in 28 countries between 2013 and 2015; patients were randomized (1:1:1) to oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (n=192), oral encorafenib 300 mg once daily (n=194), or oral vemurafenib 960 mg twice daily (n=191). The primary outcome was PFS for encorafenib plus binimetinib vs vemurafenib. Analyses were done on the intention-to-treat population. Median follow-up was 17 months. PFS was significantly increased with encorafenib plus binimetinib compared with vemurafenib (median PFS=14.9 months vs 7.3 months in the vemurafenib group; HR=0.54; 95% CI, 0.41 to 0.71; p<0.001; see Table 2). OS was not reported. The most common grade 3 or 4 adverse events were increased γ-glutamyltransferase (9%), increased creatine phosphokinase (7%), and hypertension (6%) in the encorafenib plus binimetinib group; palmoplantar erythrodysesthesia syndrome (14%), myalgia (10%), and arthralgia (9%) in the encorafenib group; and arthralgia (6%) in the vemurafenib group.

BRAF Plus MEK Inhibitors vs Immunotherapy

For patients who are *BRAF* V600 variant–positive unresectable or metastatic melanoma, guidelines have suggested that both immunotherapy and *BRAF* plus MEK inhibitors are appropriate first-line therapies. We found no RCTs directly comparing *BRAF* and MEK inhibitors with immunotherapy. Network meta-analyses providing indirect comparisons are discussed below.

Amdahl et al (2016) reported on a network meta-analysis of RCTs comparing dabrafenib plus trametinib in previously untreated patients with other first-line treatments approved by Health Canada as of February 2015 (dabrafenib, vemurafenib, trametinib, ipilimumab, dacarbazine) for submission to Canadian reimbursement authorities. Seven studies (total N=2834 patients) were included. Bayesian network meta-analyses were performed to estimate HRs for PFS and OS. The combination of dabrafenib plus trametinib was associated with prolonged PFS and OS compared with all other first-line therapies analyzed. For PFS, the HRs (95% credible interval) favoring dabrafenib plus trametinib were: 0.23 (0.18 to 0.29) vs dacarbazine; 0.32 (0.24 to 0.42) vs ipilimumab plus dacarbazine; 0.52 (0.32 to 0.83) vs trametinib; 0.57 (0.48 to 0.69) vs vemurafenib; and 0.59 (0.50 to 0.71) vs dabrafenib. For OS, the HRs (95% credible interval) were: 0.41 (0.29 to 0.56) vs dacarbazine; 0.52 (0.38 to 0.71) vs ipilimumab plus dacarbazine; 0.68 (0.47 to 0.95) vs trametinib; 0.69 (0.57 to 0.84) vs vemurafenib; and 0.72 (0.60 to 0.85) vs dabrafenib. Nivolumab, pembrolizumab, and cobimetinib were not approved in Canada when the analysis was conducted.

Devji et al (2017) performed a network meta-analyses comparing first-line treatments and including RCTs of treatment-naive patients in which at least 1 intervention was a *BRAF* and a MEK inhibitor or an immune checkpoint inhibitor. Fifteen RCTs (total N=6662 patients) were included. Treatments were combined into drug classes: targeted therapy (*BRAF* and/or MEK inhibitor), immunotherapy (cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4], programmed cell death protein 1 [PD-1], and/or granulocyte macrophage colony–stimulating factor), chemotherapy, and combinations of these treatments. Bayesian network meta-analyses

were performed to calculate HRs for OS and PFS and odds ratios for objective response rates. The risk of bias for the included studies was low. *BRAF* plus MEK inhibition and PD-1 were both individually associated with improved OS compared with all other treatments except CTLA-4/granulocyte macrophage colony–stimulating factor; there was no significant difference in OS between *BRAF* plus MEK inhibition and PD-1 (HR=1.02; 95% credible interval, 0.72 to 1.45). The network meta-analysis showed a significant advantage of *BRAF* plus MEK inhibition compared with all other treatment strategies for PFS and objective response rate. Chemotherapy and PD-1 had the lowest risk of serious adverse events.

Pasquali et al (2017) also compared immune checkpoint inhibitors with *BRAF* targeted therapies in a network meta-analysis that included 12 RCTs (total N=6207 patients) reporting on anti-PD-1 antibodies, anti-CTLA-4 antibodies, *BRAF* inhibitors, and MEK inhibitors. *BRAF* plus MEK inhibition was associated with longer PFS compared with *BRAF* inhibition alone and immunotherapy (*BRAF* plus MEK vs anti-CTLA-4, HR=0.22; 95% CI, 0.12 to 0.41; *BRAF* vs MEK vs anti-PD-1 antibodies, HR=0.38; 95% CI, 0.20 to 0.72; *BRAF* plus MEK vs *BRAF* alone, HR=0.56; 95% CI, 0.44 to 0.70). Anti-PD-1 monoclonal antibodies were estimated to be the least toxic while the combination of anti-CTLA-4 and anti-PD-1 monoclonal antibodies was associated with the highest toxicity level.

Section Summary: Clinical Validity and Clinical Usefulness

RCTs of *BRAF* and MEK inhibitor therapy in patients selected by *BRAF* V600 variant testing have shown improvements in OS and PFS. Single-agent *BRAF* inhibitor treatment with vemurafenib and dabrafenib compared with chemotherapy has shown superior outcomes for response and PFS. Combination *BRAF* and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib alone or dabrafenib alone. There are no RCTs directly comparing *BRAF* and MEK inhibitor therapy with immunotherapy as a first-line treatment for patients with *BRAF* pathogenic variants. Network meta-analyses including indirect comparisons have suggested that *BRAF* and MEK combination therapy might prolong PFS but with higher toxicity compared with immunotherapy.

Resected Stage III Melanoma

As was stated, clinical validity and clinical utility are evaluated together when treatments are developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is codeveloped to identify diseased patients with that target. Therefore, Phase 3 RCTs of targeted treatments are reviewed in this section in which either (1) testing for the *BRAF* variant was required for enrollment into the trial or (2) RCTs in which *both* patients with and without *BRAF* variants were enrolled and treatment effects stratified by variant status are reported.

Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with resected Stage III melanoma is to inform a decision whether to use adjuvant treatment with *BRAF* and/or MEK tyrosine kinase inhibitors after surgical resection. Observation, as well as treatment with nivolumab or ipilimumab, are also options for resected, Stage III melanoma. There are no RCTs directly comparing *BRAF* and MEK inhibitors with immunotherapy.

The question addressed in this evidence review is: Does testing for *BRAF* V600 pathogenic variants to select treatment improve the net health outcome in individuals with resected Stage III melanoma?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with Stage III resected melanoma.

Interventions
The cobas 4800 *BRAF* V600 test and THxID *BRAF* kit are FDA-approved companion diagnostics for selecting patients for treatment with FDA-approved *BRAF* or MEK inhibitors.

Comparators
The comparator of interest is the standard treatment for resected Stage III melanoma without genetic testing for *BRAF* variants, which includes observation, checkpoint inhibitor immunotherapy, or high-dose interferon alfa.

Outcomes
The primary outcome of interest is recurrence. False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, which have not been shown to be effective in patients without *BRAF* V600 pathogenic variants, and also could lead to delay in treatment with immunotherapy.

Timing
The time point of interest for outcomes is at least 3 years.

Setting
Patients with resected Stage III melanoma would receive care from dermatologists and oncologists.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid and Clinical Usefulness
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Two RCTs of *BRAF* and/or MEK inhibitors in patients with resected Stage III *BRAF*-variant melanoma, have been reported. Trial design characteristics are reported in Table 2; results are

reported in Table 3. An appraisal of study relevance as well as design and conduct gaps are reported in Tables 4 and 5.

Long et al (2017) reported on results of COMBI-AD, a Phase 3 RCT comparing adjuvant combination therapy using dabrafenib plus trametinib with placebo in 870 patients who had Stage III melanoma with *BRAF* V600E or V600K variants. In 2013 and 2014 when patients were being enrolled in COMBI-AD, observation was the standard of care after resection of Stage III melanoma in most countries. With a median follow-up of 2.8 years, the 3-year rate of relapse-free survival was 58% in the combination group and 39% in the placebo group (HR=0.47; 95% CI, 0.39 to 0.58; p<0.001). OS rates at 3 years were 86% and 77%, respectively (HR=0.57; 95% CI, 0.42 to 0.79; p<0.001).

Maio et al (2018) reported on results of BRIM8, a Phase 3 RCT comparing adjuvant vemurafenib monotherapy with placebo in 498 patients who had Stage IIC, IIIA, IIIB, or IIIC *BRAF* V600 variant–positive melanoma. Patients with Stage IIC, IIIA, or IIIB disease were enrolled in cohort 1 (n=314), and patients with Stage IIIC disease were enrolled in cohort 2 (n=184). As stated previously, during enrollment, observation was standard care for Stage III melanoma. A hierarchical testing strategy was prespecified for the primary outcome (disease-free survival) based on the assumption that observing a biologic effect in higher risk disease (i.e., cohort 2) would suggest a treatment effect across the continuum of melanoma given the effect is already established in metastatic melanoma. In the hierarchical strategy, only a p value of 0.05 or less in cohort 2 would allow for results in cohort 1 to be considered significant. The median trial follow-up was 34 months (interquartile range, 26-42 months) in cohort 2 and 31 months (interquartile range, 26-41 months) in cohort 1. In cohort 2, median disease-free survival was 23 months (95% CI, 19 to 27 months) in the vemurafenib group and 15 months (95% CI, 11 to 36 months) in the placebo group (HR=0.80; 95% CI, 0.54 to 1.18; p=0.26). In cohort 1, median disease-free survival was not reached (95% CI, not estimable) in the vemurafenib group and 37 months (95% CI, 21 to not estimable) in the placebo group (HR=0.54; 95% CI, 0.37 to 0.78); however, this result cannot be considered statistically significant because of the prespecified hierarchical testing strategy.

Table 2. Characteristics of RCTs of *BRAF* and/or MEK Inhibitors for *BRAF*-Positive Stage III Melanoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					BRAF and/or MEK Inhibitor	**Control**
Long et al (2017) COMBI-AD (NCT01682083)	26 countries including U.S.	169	2013-2014	Adults with completely resected stage III melanoma with *BRAF* V600E or V600K variants: • Stage IIIA: 19% • Stage IIIB: 39% • Stage IIIC 41% • Stage III unspecified: 1%	Dabrafenib (150 mg bid) plus trametinib (2 mg qd) for 12 mo (n=438)	Matching placebos (n=432)
Maio et al (2018); BRIM8 (NCT01667419)	23 countries including U.S.	124	2012-2015	• Adults with completely resected stage IIC, IIIA, or IIIB (cohort 1) or stage IIIC (cohort 2) melanoma with *BRAF* V600E or	• Cohort 1: n=157 • Cohort 2: n=93 • Vemurafenib	• Cohort 1: n=157 • Cohort 2: n=91 • Matching

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
				V600K variants • Cohort 1: ○ Stage IIC: 9% ○ Stage IIIA: 24% ○ Stage IIIB: 68% • Cohort 2: ○ Stage IIIC: 100%	(960 mg bid) for 12 mo	placebo

bid: twice daily; qd: every day; RCT: randomized controlled trial.

Table 3. Results of RCTs of *BRAF* and/or MEK Inhibitors for *BRAF*-Positive Stage III Melanoma

Study	Median Recurrence-Free Survival, mo	Distant Metastasis	Death	SAEs
	Recurrence or Death	% Over Study Period	% Over Study Period	
Long et al (2017)				
N	870	870	870	867
Dabrafenib plus trametinib (95% CI)	Not yet reached (44.5 to NE)	25%	14%	36%
Control (95% CI)	16.6 (12.7 to 22.1)	35%	22%	10%
TE (95% CI); p	HR=0.47 (0.39 to 0.58); <0.001	HR=0.51 (0.40 to 0.65); <0.001	HR=0.57 (0.42 to 0.79); <0.001	NR
	Recurrence, New Primary Melanoma, or Death	Median, mo	% at 2 Years	
Maio et al (2018)				
Cohort 1 (stage IIC, IIIA, IIIB)				
N	314	314	314	494[b]
Vemurafenib	Not yet reached (NE)	Not yet reached (NE)	93 (89% to 98%)	16%
Control	36.9 (21.4 to NE)	Not yet reached (NE)	87 (81% to 92%)	10%
TE (95% CI); p	HR=0.54 (0.37 to 0.78)[a]	HR=0.58 (0.37 to 0.90); 0.01	NR	NR
Cohort 2 (stage IIIC)				
N	184	184	184	See above[b]
Vemurafenib	23.1 (18.6 to 26.5)	37.2 (22.1 to NE)	84% (76% to 92%)	
Control	15.4 (11.1 to 35.9)	30.7 (24.5 to NE)	85% (78% to 93%)	
TE (95% CI); p	HR=0.80 (0.54 to 1.18); 0.26[a]	HR=0.91 (0.57 to 1.44); 0.68	NR	

CI: confidence interval; HR: hazard ratio; NE: not estimable; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event; TE: treatment effect.
[a] Hierarchical testing of cohort 2 before cohort 1 was prespecified for this outcome. Because the HR in cohort 2 was not statistically significantly different than 1, the test in cohort 1 cannot be regarded as significant.
[b] Cohorts 1 and 2 combined for safety analyses.

Table 4. Relevance Gaps of RCTs of *BRAF* and/or MEK Inhibitors for *BRAF*-Positive Stage III Melanoma

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Long et al (2017)			2. Trial was conducted before immunotherapy became		

	more widely used in stage III melanoma
Maio et al (2018)	2. Trial was conducted before immunotherapy became more widely used in stage III melanoma

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FU: follow-up; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 5. Study Design and Conduct Gaps of RCTs of *BRAF* and/or MEK Inhibitors for *BRAF*-Positive Stage III Melanoma

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Long et al (2017)						
Maio et al (2018)						

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i,e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Clinical Valid and Clinical Usefulness

RCTs of *BRAF* and MEK inhibitor therapy in Stage III melanoma patients selected by *BRAF* V600 variant testing have shown reductions in recurrence risk. One well-conducted RCT of combination *BRAF* and MEK inhibitor treatment with dabrafenib plus trametinib has shown superiority for recurrence risk and OS in BRAF variant-positive, Stage III patients compared with placebo. Single-agent *BRAF* inhibitor treatment using vemurafenib compared with placebo showed numeric benefit for disease-free survival in patients with Stage IIC, IIIA, or IIIB *BRAF* V600 variant-positive melanoma but this result must be considered exploratory given the lack of statistically significant benefit in Stage IIIC disease and the hierarchical statistical testing strategy. There are no RCTs directly comparing *BRAF* and MEK inhibitor therapy with immunotherapy as an adjuvant treatment for Stage III patients with *BRAF* pathogenic variants.

Glioma

When treatment is developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is co-developed to identify diseased patients with that target,

clinical validity and clinical utility cannot be evaluated separately. Rather, clinical studies of treatment benefit, which use the test to select patients, provide evidence of both clinical validity and clinical utility. We reviewed the Phase 3 clinical trials of treatments in which testing for the *BRAF* variant was required for selection into the trial. In the absence of clinical trials in which both patients with and without *BRAF* variants are entered into RCTs of novel therapies, we cannot be certain that the test has clinical utility because it is unknown whether the treatment would be effective in patients without *BRAF* variant. However, patients without *BRAF* variants have not been enrolled in clinical trials of *BRAF* inhibitors.

Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with glioma is to inform a decision whether to treat with *BRAF* or MEK inhibitors or with other standard treatments for glioma. Standard treatment for patients with glioma includes surgical resection followed by radiotherapy and/or chemotherapy with temozolomide.

The question addressed in this evidence review is: Does testing for *BRAF* pathogenic variants to select treatment improve the net health outcome in individuals with glioma?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with glioma, particularly patients for whom adjuvant therapy following resection is indicated or for whom resection is not possible.

Intervention

The intervention of is genetic testing for *BRAF* V600 pathogenic variants to select treatments.

Comparators

The comparator of interest is the standard treatment for glioma without genetic testing for *BRAF* variants.

Outcomes

The primary outcomes of interest are OS and PFS. False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, may not be effective in patients without *BRAF* V600 pathogenic variants, and could also lead to delay in treatment with chemotherapy.

Timing

For low-grade glioma, the time point of interest for survival outcomes is at least 5 years. Due to the poor prognosis of high-grade glioma, demonstration of improvement in survival outcomes at 1 year is important.

Setting
Patients diagnosed gliomas should be referred for treatment by specialists experienced in the management of glioma. This will likely consist of a multidisciplinary group of physicians including neurologists, neurosurgeons, oncologists, and radiation oncologists.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of un-published and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity and Clinical Usefulness
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Sorafenib
Sorafenib is a multikinase inhibitor with potent in vitro activity against both *BRAF* wild-type and V600E variants as well as vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and c-KIT. Several Phase 2, single-arm prospective studies have investigated the use of sorafenib in newly diagnosed and recurrent, adult and pediatric, low- and high-grade gliomas in various combinations with other treatments. Results have not shown sorafenib to be effective. Most studies did not report *BRAF* V600 variant status. Table 7 describes select prospective studies of sorafenib in glioma.

Table 6. Prospective Studies of Sorafenib in Patients With Glioma

Study	Populations	N	Treatment(s)	Results (95% CI), mo	
				Median PFS	**Median OS**
Karajannis et al (2014)	Children with recurrent or progressive low-grade astrocytomas	11 overall; 5 positive for constitutive *BRAF* activation (*KIAA-BRAF* fusion or *BRAF*-activating variant including *BRAF* V600E)	Sorafenib bid at 200 mg/m^2 per dose in continuous 28-d cycles	2.8 (2.1 to 31.0)[a]	
Hottinger et al (2014)	Adults with newly diagnosed high-grade glioma	17; *BRAF* status not reported	60-Gy RT plus TMZ 75 mg/m^2 per day and sorafenib 200 mg qd, 200 mg bid, or 400 mg bid	7.9 (5.4 to 14.6)	17.8 (14.7 to 25.6)
Galanis et al (2013)	Adults with recurrent GBM	54; *BRAF* status not reported	Bevacizumab 5 mg/kg per 2 wk plus sorafenib 200 mg qd or bid	6-mo, 20.4%	5.6 (4.7 to 8.2)
Zustovich et al (2013)[55]	Adults with recurrent GBM	53; *BRAF* status not reported	TMZ 40 mg/m^2 per day plus sorafenib 400 mg bid	3.2 (1.8 to 4.8)	7.4 (5.6 to 9)
Den et al	High-grade	18; *BRAF* status	Sorafenib 200-400 mg		18 (6 to

Study	Populations	N	Treatment(s)	Results (95% CI), mo	
(2013)	glioma (primary or recurrent) with at least 2 wk of RT	not reported	bid plus: • Primary disease, TMZ 75 mg/m^2 per day and 60-Gy RT • Recurrent disease, 35 Gy in 10 fractions		undefined)
Peereboom et al (2013)	Adults with recurrent or progressive GBM	56; *BRAF* status not reported	Erlotinib 150 mg qd plus sorafenib 400 mg bid	2.5 (1.8 to 3.7)	5.7 (4.5 to 7.9)
Lee et al (2012)	Adults with recurrent GBM or gliosarcoma	18; *BRAF* status not reported	Sorafenib 800 mg qd plus temsirolimus 25 mg/wk	8 wk (5 to 9 wk)[a]	
Hainsworth et al (2010)	Adults with newly diagnosed GBM	47; *BRAF* status not reported	60-Gy RT and TMZ 75 mg/m^2 per day followed by TMZ 150 mg/m^2 per day plus sorafenib 400 mg bid	6 (3.7 to 7)	12 (7.2 to 16)

bid: twice daily; CI: confidence interval; GBM: glioblastoma multiforme; Gy: gray; OS: overall survival; PFS: progression-free survival; qd: every day: RT: radiotherapy; TMZ: temozolomide.
[a] Study terminated early.

Vemurafenib, Dabrafenib, and Trametinib
Several case reports and small case series have suggested clinical benefit with vemurafenib, dabrafenib, and trametinib in patients with glioma and *BRAF* V600 pathogenic variants.

Hyman et al (2015) published results of a multicenter Phase 2 "basket" study of vemurafenib in *BRAF* V600 variant–positive nonmelanoma cancers. A total of 122 patients with *BRAF* V600 pathogenic variants were enrolled, including 8 patients with gliomas. The response was assessed by site investigators using RECIST criteria. Of the 8 glioma patients, 2 died before the 1-month evaluation; 4 had stable disease at 12, 6, 4, and 3 months and 2 had progressive disease at 2 and 7 months, all respectively.

Section Summary: Clinical Validity and Clinically Useful
Studies of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 status. Evaluation of the *BRAF* and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited to 1 Phase 2 "basket" study (including 8 patients with glioma), case reports, and small case series. Several early-phase studies are ongoing. Phase 3 clinical trials of targeted treatments are needed in which either (1) testing for the *BRAF* variant was required for selection into the trial or (2) patients with and without a *BRAF* variant are included, and testing for treatment interactions by variant status are prespecified.

Summary of Evidence
For individuals who have un-resectable or metastatic melanoma who receive *BRAF* gene variant testing to select treatment with *BRAF* or MEK inhibitor combination therapy, the evidence includes randomized trials. Relevant outcomes are overall survival, disease-specific survival, and

test accuracy. Randomized Phase 3 trials of *BRAF* inhibitor therapy in patients selected on the basis of *BRAF* variant testing have shown improvements in overall survival and progression-free survival. Single-agent *BRAF* inhibitor treatment compared with non-targeted treatments have shown superior outcomes for most end points. Combination *BRAF* and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior overall survival compared with vemurafenib or dabrafenib alone. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have resected Stage III melanoma who receive *BRAF* gene variant testing to select treatment with *BRAF* or MEK inhibitors, the evidence includes randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. One randomized Phase 3 trial of *BRAF* and MEK combination therapy with dabrafenib plus trametinib in patients selected by *BRAF* variant testing has shown improvements in recurrence-free survival and overall survival compared with placebo. One randomized Phase 3 trial of vemurafenib monotherapy did not find statistically significant differences in disease-free survival in patients with Stage IIIC disease. In patients with Stage IIC, IIIA, or IIIB disease, median disease-free survival was prolonged with vemurafenib, but this result was considered exploratory. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have glioma who receive *BRAF* gene variant testing to select treatment with *BRAF* or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies assessing the use of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 variant status. Evaluation of the *BRAF* and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited to a phase 2 "basket" study, including 8 patients with glioma, as well as case reports and small case series. Early reports have suggested clinical benefit, but confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network Guidelines for melanoma (v.2.2018) recommends *BRAF* variant status should be tested "using an FDA-approved [Food and Drug Administration] test or by a facility approved by CLIA [Clinical Laboratory Improvement Amendments] facility." Combination dabrafenib plus trametinib and combination vemurafenib plus cobimetinib therapies have a Category 1 recommendation as a preferred regimen for advanced or metastatic melanoma. Vemurafenib and dabrafenib also have Category 1 recommendations for advanced or metastatic melanoma. The National Comprehensive Cancer Network also recommends dabrafenib plus trametinib combination therapy as an option for patients with Stage III

melanoma who have a *BRAF* V600–activating variant and sentinel lymph node metastasis greater than 1 mm (Category 1).

NCCN guidelines for central nervous system cancers (v.1.2018) indicate the following on the use of *BRAF* molecular markers to guide treatment decisions for primary brain cancers: "*BRAF* V600E tumors may respond to *BRAF* inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:

BRAF V600E, ALK, metastatic melanoma, Zelboraf, vemurafenib, THxID *BRAF*, *BRAF* V600K, glioma

Approved by Governing Bodies:

Table 7 summarizes the targeted treatments approved by the U.S. Food and Drug Administration for patients with melanoma along with the concurrently approved diagnostic tests. The combination agent encorafenib and binimetinib (Array BioPharma) is under review for the treatment of *BRAF* variant advanced, unresectable, or metastatic melanoma with target action date of June 30, 2018. The combination agent of dabrafenib and trametinib (GlaxoSmithKline) was approved in May 2018 for adjuvant treatment of *BRAF* variant, resected, Stage III melanoma; the agent had both breakthrough therapy and priority review designations.

Table 7. FDA-Approved Targeted Treatments for Melanoma and Their Approved Companion Diagnostic Tests

Treatment	Indication	FDA Approval of Companion Diagnostic Test
Vemurafenib (Zelboraf®; Roche/Genentech and Plexxikon)	• 2011: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600 variants[34]	• 2011: cobas® 4800 BRAF V600 Mutation Test (Roche)[35] • 2017: FoundationOne CDx™ (Foundation Medicine)[36]
Dabrafenib (Tafinlar®; GlaxoSmithKline)	• 2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variants[15] • 2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants • 2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants	• 2013: THxID™ BRAF kit (bioMérieux)[35] • 2017: FoundationOne CDx™ (Foundation Medicine)[36]
Trametinib (Mekinist™; GlaxoSmithKline)	• 2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants[17] • 2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants • 2018: Used in combination with dabrafenib for	• 2013: THxID™ BRAF kit (bioMérieux)[35] • 2017: FoundationOne CDx™ (Foundation Medicine)[36]

	adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants	
Cobimetinib (Cotellic®; Genentech)	• 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variants[18]	• 2017: FoundationOne CDx™ (Foundation Medicine)[36]

FDA: Food and Drug Administration.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81210 BRAF (b-raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant

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Policy History:

Medical Policy Panel September 2011
Medical Policy Group, September 2011 **(1):** 2011 Added coverage criteria for BRAF mutation testing related to vemurafenib
Medical Policy Administration Committee, October 2011
Available for comment October 19 through December 5, 2011
Medical Policy Panel, October 2012
Medical Policy Group, October 2012 **(1):** 2012 Update to Key Points and References; no change to policy statement
Medical Policy Panel, October 2013
Medical Policy Group, October 2013 **(1):** 2013 Update to Description, Key Points, Governing Bodies and References; no change to policy statement
Medical Policy Group, January 2014 **(1):** Creation of individual policy with all references related to BRAF testing removed from medical policy #133; no change to policy statement
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 **(1):** 2014 Update to Description, Key Points, and Practice Guidelines. No Policy change, but did revise statement to align with current FDA-approved indication, i.e. "unresectable or metastatic" rather than "Stage IIIC or IV.
Medical Policy Group, November 2015: 2016 Annual Coding Update. Revised CPT code 81210.
Medical Policy Panel, December 2015
Medical Policy Group, January 2016 **(3):** 2016 Updates to Key Points and References. No change to policy statement.
Medical Policy Panel, June 2017
Medical Policy Group, August 2017 **(3):** 2017 Updates to Title, Description, Key Points, Approved by Governing Bodies & References; Policy statements updated.
Medical Policy Administration Committee, August 2017
Available for comment August 5 through September 18, 2017
Medical Policy Panel, June 2018
Medical Policy Group, July 2018 **(3):** Updates to Title, Description, Key Points, Approved by Governing Bodies, and References. Removed Previous Coding deleted 01/01/2013. Policy section updated with criteria for *BRAF* testing in resected Stage III melanoma as medically necessary.
Available for comment August 7, 2018 through September 21, 2018.
