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

Policy Number: 2.04.77  Last Review: 12/2017
Origination: 4/2013  Next Review: 12/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for BRAF gene mutation testing to select melanoma patients for BRAF inhibitor targeted therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Testing for the BRAF V600 mutation in tumor tissue of patients with unresectable or metastatic melanoma may be considered medically necessary to select patients for treatment with FDA-approved BRAF inhibitors. (see Considerations)

When Policy Topic is not covered
Testing for the BRAF V600 mutation for all other patients with melanoma, including but not limited to, use in patients with resectable melanoma, is considered investigational.

Testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment is considered investigational.

Considerations
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.

FDA-approved BRAF testing kits are intended to select melanoma patients for treatment with vemurafenib, dabrafenib, trametinib, and cobimetinib. Prescribing information for these drugs states that confirmation of BRAF V600 variants using an FDA-approved test is required for selection of patients with melanoma appropriate for therapy.
Pivotal trials for vemurafenib, dabrafenib, trametinib, and cobimetinib have enrolled patients with unresectable, stage III or IV melanoma.

**Genetics Nomenclature Update**
Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

There is a specific CPT code:
81210: **BRAF (B-Raf proto-oncogene, serine/threonine kinase)** (eg, colon cancer, melanoma), gene analysis, V600 variant(s)

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With unresectable or metastatic melanoma</td>
<td>Interventions of interest are: <strong>BRAF</strong> gene variant testing to select treatment with <strong>BRAF</strong></td>
<td>Comparators of interest are: Standard treatment without genetic testing</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival</td>
</tr>
</tbody>
</table>
BRAF inhibitors are drugs designed to target a somatic mutation in the *BRAF* gene of patients with advanced melanoma. BRAF codes for a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. The mutated version of the BRAF kinase results in constitutive activity, which is believed to be actively involved in oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to significantly retard tumor growth and may improve patient survival.

For individuals who have unresectable or metastatic melanoma who receive *BRAF* gene variant testing to select treatment with BRAF or MEK inhibitors, the evidence includes studies of analytic validity and randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies of analytic validity have shown that *BRAF* variant testing kits have high concordance with the reference standard (Sanger sequencing). 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 nontargeted 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 either 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 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 1 phase 2 “basket” study, including 8 patients with glioma, 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.
**Background**

**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; 5-year survival is 15% to 20%.

**Treatment**

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 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. 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 one potential first-line treatment of metastatic or unresectable melanoma by the National Comprehensive Cancer Network; the Network no longer recommends cytotoxic chemotherapy for first-line treatment.

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 [also called MAPK] 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 and 2 MEK inhibitors 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 demonstrated that vemurafenib selectively blocked the MAPK 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 the \(BRAF\) kinase, with greatest activity against V600E-
mutated BRAF. In vitro and in vivo studies have demonstrated dabrafenib’s ability to inhibit growth of BRAF V600-variant 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 growth of BRAF V600 variant-positive melanoma cells in vitro and in vivo.

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

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.

Treatment
Low-grade gliomas were historically 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 radiation 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 MAPK pathway, particularly in patients with high-grade glioma and low-grade gliomas whose tumors are in locations that
prevent full resection or recurrent. 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.\textsuperscript{30, 31} indicating that these agents might be potential therapies for primary brain tumors.

**Regulatory Status**

In August 2011, vemurafenib (Zelboraf\textsuperscript{®}; Roche/Genentech and Plexxikon) and a class III companion diagnostic test, the cobas\textsuperscript{®} 4800 BRAF V600 Mutation Test (Roche), were coapproved by the U.S. Food and Drug Administration (FDA). The cobas\textsuperscript{®} 4800 BRAF V600 test was approved through the premarket approval process as an aid in selecting melanoma patients whose tumors carry BRAF V600 variants for treatment with vemurafenib.\textsuperscript{32} Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 variants. Vemurafenib’s prescribing information states that confirmation of the BRAF V600 variants using an FDA-approved test is required to select patients appropriate for therapy.\textsuperscript{33}

In May 2013, dabrafenib (Tafinlar\textsuperscript{®}; GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E variants, as detected by an FDA-approved test. Dabrafenib is specifically not indicated to treat patients with wild-type BRAF melanoma.\textsuperscript{16}

In May 2013, trametinib (Mekinist\textsuperscript{™}; GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test. Trametinib is specifically not indicated to treat patients who previously received BRAF inhibitor therapy.\textsuperscript{18}

The companion diagnostic test coapproved for both dabrafenib and trametinib is the THxID\textsuperscript{™} BRAF kit (bioMérieux). The kit is intended “as an aid in selecting melanoma patients whose tumors carry the BRAF V600E variants for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K variants for treatment with trametinib.”\textsuperscript{32}

In January 2014, the combination of dabrafenib (Tafinlar\textsuperscript{®}) and trametinib (Mekinist\textsuperscript{™}; both GlaxoSmithKline) were approved by FDA through the accelerated approval process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test. Approval was based on response rather than survival outcomes observed in the phase 1/2 trial described next (see Rationale section).\textsuperscript{16, 18} Continued approval is contingent on results from a phase 3 trial comparing combination therapy with dabrafenib monotherapy in patients with metastatic or unresectable melanoma.

In December 2015, cobimetinib (Cotellic\textsuperscript{®}; Genentech) was approved by FDA after priority review for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K variants, in combination with vemurafenib.\textsuperscript{19}
Rationale

Literature Review

This evidence review was originally created in October 2011 and has been updated regularly with searches of the MEDLINE database. The original review was informed by a 2011 TEC Special Report. For the Special Report, the MEDLINE database was searched (via PubMed) for articles using the terms “PLX4032,” “vemurafenib,” “V600E,” and “BRAF inhibitor,” all coupled with the term “melanoma.” Reference lists of relevant study publications and review articles also were examined. Meeting abstracts for the 2011 annual meeting of the American Society of Clinical Oncology were searched using the MEDLINE search terms. If available, virtual presentations and slides were reviewed for key abstracts. The grey literature was consulted in the form of drug and laboratory test approval information released by the U.S. Food and Drug Administration (FDA), ongoing clinical trials (at www.ClinicalTrials.gov), and online searches for status and ancillary information. The most recent literature review was performed through April 25, 2017 (see Appendix Table 1 for genetic testing categories).

Since the TEC Special Report, additional phase 3 randomized controlled trials (RCTs) have been published. These trials, which evaluated treatment with dabrafenib, trametinib, and cobimetinib for advanced melanoma in BRAF-positive patients, are also presented.

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (ie, a demonstration that the diagnostic information can be used to improve patient health outcomes). Following is a summary of the key publications and regulatory documents to date.

Melanoma

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 and/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 (eg, 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 is 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 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 FDA-approved companion diagnostics for selecting patients for treatment with FDA-approved BRAF or MEK inhibitors.

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

**Outcomes**
The primary outcomes of interest are overall survival and progression-free survival. 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.

**Time**
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.

**Analytic Validity**
The analytic validity of a genetic test is its ability to accurately and reliably measure the genotype (or analyte) of interest in the clinical laboratory, and in specimens representative of the population of interest. Submission to the FDA Office of In Vitro Diagnostics for marketing clearance or approval of a diagnostic test requires an extensive demonstration of the analytic validity of the test. Data for cleared or approved tests are summarized in the kit insert (prepared by the
manufacturer) and in the summary of safety and effectiveness data of the test (prepared by FDA and publicly available). Analytic validity of FDA-approved BRAF variant tests has been assessed in several studies where the results of the test have been correlated with Sanger sequencing. Immunohistochemical (IHC) analysis of BRAF status is also available.

**Cobas 4800 BRAF V600 Variant Test**

The cobas 4800 BRAF V600 Mutation Test is a real-time polymerase chain reaction (PCR) test intended for the qualitative detection of the BRAF V600E variant specifically in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) human melanoma tissue.

Correlation between the cobas 4800 BRAF V600 Mutation Test results and Sanger sequencing was tested in the phase 3 trial of vemurafenib in 596 consecutive patients, 439 of whom were evaluable. The percentage agreement between the BRAF V600 Mutation Test and Sanger sequencing is shown in the line 3 of Table 1 where only V600E results were counted as positive. The cobas 4800 BRAF V600 Mutation Test detected 27 V600 variants (primarily V600K) that were not V600E by Sanger sequencing. Limited evidence suggests that patients with V600K-variant tumors may also respond to vemurafenib.

Tumor specimens from patients enrolled in the phase 2 trial were also sequenced by Sanger sequencing; specimens that were invalid by Sanger, or that were identified as V600K mutated or as V600 wild-type by Sanger, were resequenced by the more sensitive 454 pyrosequencing method to resolve differences. Correlation with 454 pyrosequencing was 100% if V600K-positive samples were counted as true positives (see Table 1).

Tumor specimens from 55 patients enrolled in a phase 1 clinical trial of vemurafenib were subjected to cobas 4800 BRAF V600 Mutation Test and to Sanger sequencing. The limit of detection with the cobas 4800 BRAF V600 Mutation Test was 5% mutant allele and 20% with Sanger sequencing. The cobas 4800 BRAF Mutation Test was found to be highly predictive for V600E; however, it also detected other BRAF V600 variants (V600K; 65.8% agreement with Sanger sequencing, V600D, V600E2, and V600R; not determined) with less sensitivity. Data for study 3 are presented in Table 1.

Halait et al (2012) assessed the analytical performance of the cobas 4800 BRAF V600 Mutation Test and Sanger sequencing in 219 melanoma specimens. A correct call rate greater than 96% was obtained across all specimen types with 5% variant sequences. The cobas 4800 BRAF V600 Mutation Test and Sanger sequencing correlation results for V600E in study 4 are presented in Table 1. After discrepant analysis with 454 pyrosequencing, the positive percent agreement increased to 100%, the negative percent agreement increased to 93%, and the overall percent agreement increased to 96%.

A similar study by Anderson et al (2012) used screening specimens from phase 2 and 3 trials of vemurafenib. Of 477 available specimens, 433 had both a valid
cobas and valid Sanger sequencing results. Correlation results were similar to those obtained by Halait et al (2012) and are shown in Table 1. Of 42 discordant results (cobas variant–positive and Sanger V600E–negative), 17 (40%) were V600E-positive and 24 (57%) were V600K-positive by 454 pyrosequencing; 1 sample with a V600D variant on Sanger sequencing was wild-type by 454 pyrosequencing. Reproducibility was assessed across 3 sites. Correct interpretations were made for all wild-type specimens and for specimens with more than 5% mutant allele, the limit of detection of the cobas test.

Regulatory documents provide additional data detailing the evaluation of analytic sensitivity and specificity, cross-reactivity, interference, reproducibility, repeatability, and additional studies of test robustness. In general, correlation with sequencing and extensive analytic validation data support that the test is a sensitive, specific, and robust assay for the detection of the V600E variant in melanoma specimens. Patients with V600K variants will also be identified as positive, although it is unclear whether all patients with V600K variants will be positive. There is very limited evidence that patients with V600K variants may respond to vemurafenib. Infrequently, patients with V600E2 and V600D variants may also be detected. Additionally, the method is available as a kit and is partially automated, which should result in wide access and rapid turnaround time relative to the reference standard of sequencing.

Table 1. Correlation of the cobas 4800 BRAF V600 Mutation Test Results With Sanger Sequencing

<table>
<thead>
<tr>
<th>Definition of Positive</th>
<th>Positive % Agreement</th>
<th>Negative % Agreement</th>
<th>Overall % Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 3 trial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only V600E</td>
<td>97.3</td>
<td>84.6</td>
<td>90.9</td>
</tr>
<tr>
<td>All V600</td>
<td>87.7</td>
<td>95.4</td>
<td>90.6</td>
</tr>
<tr>
<td>V600E + V600K</td>
<td>92.7</td>
<td>95.2</td>
<td>91.1</td>
</tr>
<tr>
<td><strong>Phase 2 trial</strong></td>
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</tr>
<tr>
<td>Only V600E</td>
<td>92.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V600E + V600K</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 1 trial</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Only V600E</td>
<td>97.3</td>
<td></td>
<td></td>
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<tr>
<td><strong>Analytic performance trials</strong></td>
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<tr>
<td>Only V600E</td>
<td>96</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>Only V600E</td>
<td>96.4</td>
<td>80</td>
<td>88.5</td>
</tr>
</tbody>
</table>

**THxID BRAF Kit**

The THxID BRAF kit is a real-time PCR test intended for the qualitative detection of BRAF V600E and V600K variants in DNA samples extracted from FFPE human melanoma tissue. Two oligonucleotide probes labeled with different fluorescent dyes (one for internal controls, the other for variant sequence alleles) are measured at characteristic wavelengths and compared by an autoanalyzer. Results are reported as either “mutation(s) detected” or “mutation(s) not detected” (or “invalid,” which requires troubleshooting and a repeat of the test). The threshold of detection, defined as the smallest proportion of mutated alleles for which the assay yields a positive result in 95% of tests, is 5% for V600E and V600K variants.
Correlation between the THxID BRAF assay and Sanger sequencing was tested in 898 consecutive clinical trial samples. Forty-three (5%) samples were not evaluable. Excluding these samples, there were 35 (4%) discordant cases. The THxID BRAF kit detected as V600E variant-positive 2 samples determined by Sanger sequencing to be V600D variant-positive. Additional results are shown in Table 2.

**Table 2. Correlation of THxID BRAF Kit Results With Sanger Sequencing**

<table>
<thead>
<tr>
<th>Sanger Sequencing</th>
<th>Overall Agreement</th>
<th>V600E and V600K</th>
<th>V600E</th>
<th>V600K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPA</td>
<td>NPA</td>
<td>PPA</td>
<td>NPA</td>
</tr>
<tr>
<td>Including invalids and QNS</td>
<td>92.3</td>
<td>96.4</td>
<td>89.9</td>
<td>96.3</td>
</tr>
<tr>
<td>Excluding invalids and QNS</td>
<td>95.9</td>
<td>98.1</td>
<td>93.9</td>
<td>NR</td>
</tr>
</tbody>
</table>

NPA: negative percent agreement; NR: not reported; PPA: positive percent agreement; QNS: quantity not sufficient.

**IHC Analysis**

IHC analysis is potentially a cheaper, more efficient alternative to DNA-based testing, particularly in laboratories without access to DNA-based testing. A BRAF V600E monoclonal antibody (VE1) has been developed.

Anwar et al (2016) reported on a systematic review and meta-analysis of 21 studies (total N=1687 patients) comparing VE1 IHC to DNA-based methods for identification of *BRAF* V600E variants in melanoma tissue specimens. The studies used varying cutoffs for identifying VE1 IHC as positive, and there was high heterogeneity observed between studies (I²=95%, p<0.001). The pooled sensitivity and specificity of VE1 IHC for *BRAF* V600E detection were 96% (95% confidence interval [CI], 94% to 98%) and 100% (95% CI, 97% to 100%), respectively. The area under the receiver operating characteristic curve was 0.99 (95% CI, 0.98 to 1.00). Subsequent studies have similarly reported high concordance between VE1 IHC and DNA-based testing.

**Section Summary: Analytic Validity**

The analytic validity of *BRAF* genetic tests that are FDA-approved has been described in FDA documents. Detection of *BRAF* V600E by IHC has been shown to have very high concordance with DNA-based testing.

**Clinical Validity and Clinical Utility**

The clinical validity of a genetic test is its ability to accurately and reliably predict the clinically defined disorder or phenotype of interest; the clinical utility of a genetic test is the evidence of improved measurable clinical outcomes and its usefulness and added value to patient management decision making compared with current management without genetic testing.

When a treatment is 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, 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 \textit{BRAF} variant was required for selection into the trial. In the absence of clinical trials in which \textit{both} patients with and without \textit{BRAF} variants are entered into randomized controlled trials 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 \textit{BRAF} variant. However, patients without \textit{BRAF} variants have not been enrolled in clinical trials of \textit{BRAF} inhibitors.

\textbf{Vemurafenib}

The primary evidence of clinical validity and utility for the cobas 4800 \textit{BRAF} V600 Mutation Test is provided by the phase 3 clinical trial of vemurafenib that enrolled patients who were positive for a V600 variant.

The BRIM-3 trial is summarized in Table 3. 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 overall survival (OS) or progression-free survival (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 \textit{BRAF} V600E variant on the cobas 4800 \textit{BRAF} V600 Mutation Test. Included were 19 patients with \textit{BRAF} V600K variants and 1 with a \textit{BRAF} V600D variant.

Tumor assessments, including computed tomography, were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter. Tumor responses were determined by investigators using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, criteria. 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\% 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 \textit{BRAF} V600 Mutation Test, resulting in coapproval of both the drug and companion test.

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
\textbf{Study/Year} & \textbf{FU, mo} & \textbf{Group} & \textbf{N} & \textbf{OS (95\% CI), mo} & \textbf{PFS (95\% CI), mo} & \textbf{ORR (95\% CI)} \\
\hline
\end{tabular}
\caption{Phase 3 RCTs of \textit{BRAF} and MEK Inhibitors for \textit{BRAF}-Positive Advanced Melanoma}
\end{table}
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>FU, mo</th>
<th>Group</th>
<th>N</th>
<th>OS (95% CI)</th>
<th>PFS (95% CI), mo</th>
<th>ORR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Vemurafenib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapman et al (2011)</td>
<td>6</td>
<td>Vemurafenib</td>
<td>337</td>
<td>84% (78% to 89%)</td>
<td>5.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48% (42% to 55%)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td></td>
<td></td>
<td>338</td>
<td>65% (56% to 73%)</td>
<td>1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5% (3% to 9%)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.37 (0.26 to 0.55)</td>
<td>0.26 (0.20 to 0.33)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dabrafenib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauschild et al (2012)</td>
<td>4.9&lt;sup&gt;a&lt;/sup&gt; 0-9.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dabrafenib</td>
<td>187</td>
<td>89%</td>
<td>5.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50% (42.4% to 57.1%)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td></td>
<td></td>
<td>63</td>
<td>86%</td>
<td>2.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6% (1.8% to 15.5%)</td>
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<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.61 (0.25 to 1.48)</td>
<td>0.33 (0.20 to 0.54)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Trametinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaherty et al (2012)</td>
<td>6</td>
<td>Trametinib</td>
<td>214</td>
<td>81%</td>
<td>4.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22% (17% to 28%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td>108</td>
<td>67%</td>
<td>1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8% (4% to 15%)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.54 (0.32 to 0.92)</td>
<td>0.47 (0.34 to 0.65)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dabrafenib plus trametinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long et al (2015)</td>
<td></td>
<td>Dabrafenib plus trametinib</td>
<td>211</td>
<td>74%</td>
<td>11.0</td>
<td>NA</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td></td>
<td></td>
<td>212</td>
<td>68%</td>
<td>8.8</td>
<td>NA</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.71 (0.55 to 0.92)</td>
<td>0.67 (0.53 to 0.84)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.0004</td>
<td>NA</td>
</tr>
<tr>
<td>Robert et al (2015)</td>
<td>NR</td>
<td>Dabrafenib plus trametinib</td>
<td>352</td>
<td>72%</td>
<td>11.4</td>
<td>64%</td>
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<tr>
<td>Vemurafenib</td>
<td></td>
<td></td>
<td>352</td>
<td>65%</td>
<td>7.3</td>
<td>51%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.69 (0.53 to 0.89)</td>
<td>0.56 (0.46 to 0.69)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Vemurafenib plus cobimetinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascierto et al (2016)</td>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vemurafenib plus cobimetinib</td>
<td>248</td>
<td>22.3% (20.3% to NE)</td>
<td>12.3 (9.5 to 13.4)</td>
<td>68% (61% to 73%)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td></td>
<td></td>
<td>247</td>
<td>17.4% (15.0% to 19.8%)</td>
<td>7.2 (5.6 to 7.5)</td>
<td>45% (38% to 51%)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td>0.70 (0.55 to 0.90)</td>
<td>0.58 (0.46 to 0.72)</td>
<td>NA</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FU: follow-up; IV: intravenous; 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.

<sup>a</sup> Median value.
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 3. The main objective of this RCT was to compare the efficacy of dabrafenib to standard dacarbazine treatment in patients with BRAF V600E-mutated metastatic melanoma. Two hundred fifty patients were randomized 3:1 to oral dabrafenib 150 mg twice daily or to intravenous dacarbazine 1000 mg/m² 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 greater 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 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).

The analytic validity of the THxID BRAF test kit was validated by comparing outcomes for patients identified by the test kit with outcomes for patients identified by an assay performed at a central lab. Of 250 patients enrolled in the trial, specimens from 237 patients (177 [95%] in the dabrafenib arm, 55 [87%] in the dacarbazine arm) were retested with the THxID BRAF kit. Reanalysis of the primary end point (PFS) in patients who were V600E-positive by the THxID BRAF kit showed a treatment effect that was nearly identical to that of patients identified by central assay.

Trametinib

Clinical efficacy and safety of trametinib were assessed in the phase 3, open-label METRIC trial. Patients with stage IV or unresectable stage IIIC cutaneous melanoma were randomized 2:1 to trametinib 2 mg orally once daily (n=214) or to chemotherapy (n=108), either dacarbazine 1000 mg/m² IV every 3 weeks or paclitaxel 175 mg/m² IV every 3 weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy end point was PFS; secondary end points included OS, overall response rate, and safety. Tumor
assessments were performed at baseline and at 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 3). 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.

The analytic validity of the THxID BRAF kit was demonstrated by comparing patient outcomes identified by the kit to those identified by a central lab assay. Reanalysis of PFS in patients who were V600E or V600K-positive by the THxID BRAF kit showed a treatment effect that was almost identical to the overall result in patients identified by central assay. Additional analysis for discordant results, assuming a worst case scenario as above, yielded a hazard ratio of 0.48 (95% CI, 0.35 to 0.63).

**Combination BRAF and MEK Inhibitors**

*Dabrafenib and Trametinib*

The efficacy of combination dabrafenib plus trametinib treatment has been established with 2 phase 3 clinical trials.\(^{48,49,52}\)

Combination dabrafenib plus trametinib was evaluated in the phase 3 open-label trial by Long et al.\(^{48,52}\) 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 to dabrafenib plus placebo. The primary end point was PFS, reported in a first publication,\(^{52}\) followed by a second publication in which longer term OS was reported.\(^{48}\)

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 compared dabrafenib plus trametinib to vemurafenib. A total of 704 patients with metastatic melanoma with BRAF V600E or V600K variants were randomized equally. The study 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). 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 and 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. PFS was significantly increased with vemurafenib plus cobimetinib compared to 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.

**BRAF and MEK Inhibitors vs Immunotherapy**

For patients who are BRAF V600 variant–positive unresectable or metastatic melanoma, NCCN has suggested that both immunotherapy and BRAF and 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 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 hazard ratios for PFS and OS. The combination of dabrafenib plus trametinib was
associated with prolonged PFS and OS compared to all other first-line therapies included in analysis. For PFS, the hazard ratios (95% credible interval [CrI]) favoring dabrafenib plus trametinib were: 0.23 (0.18 to 0.29) versus dacarbazine; 0.32 (0.24 to 0.42) versus ipilimumab plus dacarbazine; 0.52 (0.32 to 0.83) versus trametinib; 0.57 (0.48 to 0.69) versus vemurafenib; and 0.59 (0.50 to 0.71) versus dabrafenib. For OS, the hazard ratios were: 0.41 (0.29 to 0.56) versus dacarbazine; 0.52 (0.38 to 0.71) versus ipilimumab plus dacarbazine; 0.68 (0.47 to 0.95) versus trametinib; 0.69 (0.57 to 0.84) versus vemurafenib; and 0.72 (0.60 to 0.85) versus 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. 54 Fifteen RCTs (total N=6662 patients) were included. Treatments were combined into drug class: 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 [GM-CSF]), chemotherapy, and combinations of these treatments. Bayesian network meta-analyses were performed to calculate hazard ratios 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/GM-CSF; there was no significant difference in OS between BRAF plus MEK inhibition and PD-1 (HR=1.02; 95% CrI, 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 ORR. 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-PD1 antibodies, anti-CTLA-4 antibodies, BRAF inhibitors, and MEK inhibitors. 55 BRAF plus MEK inhibition was associated with longer PFS compared to 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-PD1 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-PD1 monoclonal antibodies were estimated to be the least toxic while the combination of anti-CTLA-4 and anti-PD1 monoclonal antibodies were associated with the most toxicity.

Section Summary: Clinical Validity and Clinical Utility

RCTs of BRAF and MET inhibitor therapy in patients selected on the basis of 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 has shown superior OS when compared with either vemurafenib or dabrafenib alone. There are no RCTs directly comparing BRAF and MEK inhibitor
therapy with immunotherapy as first-line treatment for patients with \textit{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 to immunotherapy.

**Glioma**

**Clinical Context and Test Purpose**  
The purpose of testing for \textit{BRAF} pathogenic variants in individuals with glioma is to inform a decision whether to treat with BRAF and/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 \textit{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.

**Interventions**  
The intervention of is genetic testing for \textit{BRAF} V600 pathogenic variants to select treatments.

**Comparators**  
The comparator of interest is standard treatment for glioma without genetic testing for \textit{BRAF} variants.

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

**Time**  
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 management of glioma. This will likely consist of a multidisciplinary
group of physicians including neurologists, neurosurgeons, oncologists, and radiation oncologists.

**Analytic Validity**
Currently there is no standard method for testing *BRAF* status in neuropathology. DNA-based tests for melanomas and IHC are used. The analytic validity of these methods is described in the previous section on melanoma.

**Clinical Validity and Clinical Utility**

**Sorafenib**
Sorafenib is a multikinase inhibitor with potent in vitro activity against both *BRAF* wild-type and V600E variant as well as vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), 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 4 describes select prospective studies of sorafenib in glioma.

**Table 4. Prospective Studies of Sorafenib in Patients With Glioma**

<table>
<thead>
<tr>
<th>Author et al (Year)</th>
<th>Populations</th>
<th>N</th>
<th>Treatment(s)</th>
<th>Results (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karajannis et al (2014)</td>
<td>Children with recurrent or progressive low-grade astrocytomas</td>
<td>11 overall; 5 positive for constitutive <em>BRAF</em> activation (<em>KIAA-BRAF</em> fusion or <em>BRAF</em>-activating variant including <em>BRAF</em> V600E)</td>
<td>Sorafenib bid at 200 mg/m² per dose in continuous 28-d cycles</td>
<td>Median PFS: 2.8 (2.1 to 31.0)</td>
</tr>
<tr>
<td>Hottinger et al (2014)</td>
<td>Adults with newly diagnosed high-grade glioma</td>
<td>17; <em>BRAF</em> status not reported</td>
<td>60-Gy RT plus TMZ 75 mg/m² per day and sorafenib 200 mg qd, 200 mg bid, or 400 mg bid</td>
<td>Median PFS: 7.9 (5.4 to 14.6)</td>
</tr>
<tr>
<td>Galanis et al (2013)</td>
<td>Adults with recurrent GBM</td>
<td>54; <em>BRAF</em> status not reported</td>
<td>Bevacizumab 5 mg/kg per 2 wk plus sorafenib 200 mg qd or bid</td>
<td>Six-mo, 20.4%</td>
</tr>
<tr>
<td>Zustovich et al (2013)</td>
<td>Adults with recurrent GBM</td>
<td>53; <em>BRAF</em> status not reported</td>
<td>TMZ 40 mg/m² per day plus sorafenib 400 mg bid</td>
<td>3.2 (1.8 to 4.8)</td>
</tr>
<tr>
<td>Den et al (2013)</td>
<td>High-grade glioma (primary or recurrent) with at least 2 wk RT</td>
<td>18; <em>BRAF</em> status not reported</td>
<td>Sorafenib 200-400 mg bid plus: Primary disease, TMZ 75 mg/m² per day and 60-</td>
<td>18 (6 to undefined)</td>
</tr>
</tbody>
</table>
### 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. Early-phase studies evaluating BRAF and MEK inhibitors are listed in Table 5.

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. 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 Clinical Utility

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.

### Summary of Evidence

For individuals who have unresectable or metastatic melanoma who receive *BRAF* gene variant testing to select treatment with BRAF or MEK inhibitors, the evidence includes studies of analytic validity and randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies of analytic validity have shown that *BRAF* variant testing kits have high concordance with the reference standard (Sanger sequencing). 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 nontargeted 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 either 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 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 1 phase 2 "basket" study, including 8 patients with glioma, 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.

Supplemental Information

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines for melanoma (v.1.2017) recommend BRAF-targeted therapy "only for patients with V600 mutation of the BRAF gene, as documented by an FDA-approved [Food and Drug Administration] or CLIA-approved [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.

NCCN guidelines for central nervous system cancers (v.1.2016) does not discuss BRAF-targeted therapy for primary brain cancers.

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

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
### Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 5.

#### Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT01682083a</td>
<td>COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBInation With Trametinib (GSK1120212) Versus Two Placebos in the ADjvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection</td>
<td>852</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT01909453a</td>
<td>A 2-part Phase III Randomized, Open Label, Multicenter Study of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma (COLUMBUS)</td>
<td>921</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02224781</td>
<td>A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Mutant Melanoma</td>
<td>300</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>NCT01667419a</td>
<td>A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients With Surgically Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence</td>
<td>503</td>
<td>Oct 2020</td>
</tr>
<tr>
<td><strong>Glioma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01677741a</td>
<td>Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced BRAF V600-Mutation Positive Solid Tumors</td>
<td>86</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT01089101</td>
<td>A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma</td>
<td>135</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01089101</td>
<td>A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma</td>
<td>135</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01748149a</td>
<td>PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of BRAFV600E, in Children and Young Adults With Recurrent/Refractory BRAFV600E- or BRAF Ins T Mutant Brain Tumors</td>
<td>54</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>NCT02285439</td>
<td>Phase I Study of MEK162 for Children With Progressive or Recurrent Cancer and a Phase II Study for Children With Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors</td>
<td>80</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT02034110a</td>
<td>A Phase II, Open-label, Study in Subjects With BRAF V600E-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and</td>
<td>225</td>
<td>Aug 2020</td>
</tr>
</tbody>
</table>
Safety of the Combination Therapy of Dabrafenib and Trametinib

NCT02684058a Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib Treatment in Children and Adolescent Patients With BRAF V600 Mutation Positive Relapsed or Refractory High Grade Glioma (HGG)

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


Billing Coding/Physician Documentation Information

81210  BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant

ICD-10 Codes
C43.0-  Malignant melanoma of skin code range
C43.9

Additional Policy Key Words
Genetic testing

Policy Implementation/Update Information
4/1/03  New policy; may be medically necessary.
12/1/13  Policy Guidelines corrected to eliminate the sentence that states that there is no specific CPT code. No other policy statement changes.
12/1/14  The policy statements were revised to align with the current FDA-approved indication, i.e., "unresectable or metastatic" rather than "stage IIIC or IV." Changed "lesser stage" to "resectable melanoma" in investigational statement.
12/1/15  No policy statement changes.
2/1/16   No policy statement changes.
12/1/16   No policy statement changes.
12/1/17  Policy revised with updated genetics nomenclature. Information about FDA-approved MEK inhibitor (cobimetinib) added. New policy statement stating BRAF testing in glioma is investigational was added. Policy title changed to "BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy".

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