



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider testing for *BRAF V600* variants in tumor tissue of patients with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA)-approved BRAF or MEK inhibitors to be **eligible for coverage**.

Based on review of available data, the Company may consider testing for BRAF V600 variants in tumor tissue of patients with resected stage III melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF or MEK inhibitors to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for *BRAF V600* variants for all other patients with melanoma to be **investigational**.*

Based on review of available data, the Company considers testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment to be **investigational**.*

Policy Guidelines

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society 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. The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

organizations, in addition to 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

| Previous | Updated | Definition |
|----------|----------------------------|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

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

| Variant Classification | Definition |
|-----------------------------------|--|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |
| Benign | Benign change in the DNA sequence |

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

Background/Overview

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

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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 the BRAF kinase, with the greatest activity against V600E-mutated *BRAF*. In vitro and in vivo studies have demonstrated dabrafenib's ability to inhibit the 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 the 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 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Table 1 summarizes the targeted treatments approved by the U.S. FDA 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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

(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 1. 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) | <ul style="list-style-type: none"> 2011: treatment of patients with unresectable or metastatic melanoma with <i>BRAF</i> V600 variants³⁴ | <ul style="list-style-type: none"> 2011: cobas® 4800 <i>BRAF</i> V600 Mutation Test (Roche)³⁵ 2017: FoundationOne CDx™ (Foundation Medicine)³⁶ |
| Dabrafenib (Tafinlar®; GlaxoSmithKline) | <ul style="list-style-type: none"> 2013: treatment of patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E variants¹⁵ 2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K variants 2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with <i>BRAF</i> V600E or V600K variants | <ul style="list-style-type: none"> 2013: THxID™ <i>BRAF</i> kit (bioMérieux)³⁵ 2017: FoundationOne CDx™ (Foundation Medicine)³⁶ |
| Trametinib (Mekinist™; GlaxoSmithKline) | <ul style="list-style-type: none"> 2013: treatment of patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K variants¹⁷ 2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K variants 2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with <i>BRAF</i> V600E or V600K variants | <ul style="list-style-type: none"> 2013: THxID™ <i>BRAF</i> kit (bioMérieux)³⁵ 2017: FoundationOne CDx™ (Foundation Medicine)³⁶ |
| Cobimetinib (Cotellic®; Genentech) | <ul style="list-style-type: none"> 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a <i>BRAF</i> V600E or V600K variants¹⁸ | <ul style="list-style-type: none"> 2017: FoundationOne CDx™ (Foundation Medicine)³⁶ |

FDA: Food and Drug Administration.

FDA product code: OWD.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 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 *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 (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 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. FDA for selecting patients for treatment with FDA-approved BRAF or MEK inhibitors.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 2. A total of 675 patients were randomized to vemurafenib (960 mg twice daily orally) or to dacarbazine (1000 mg/m² 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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
 Original Effective Date: 11/16/2011
 Current Effective Date: 08/15/2018

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 coproapproval 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 2. 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%) |
| | | 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 ^c | 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 |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

| Study/Year | FU, mo | Group | N | OS (95% CI) | PFS (95% CI), mo | ORR (95% CI) | |
|-------------------------------------|-----------------|------------------------------|-----|------------------------|---------------------|------------------|--------|
| | | | | 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.

^aMedian value.

^bRange.

^cEither intravenous dacarbazine 1000 mg/m² or intravenous paclitaxel 175 mg/m² every 3 weeks at investigator discretion.

^dCompared 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 2. 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/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 higher in the dabrafenib group (50%; 95% CI, 42.4%

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 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 intravenously every 3 weeks or paclitaxel 175 mg/m² intravenously 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 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 2). 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 group 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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 2). 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 2). 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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-naïve 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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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?

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
 Original Effective Date: 11/16/2011
 Current Effective Date: 08/15/2018

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 3; results are reported in Table 4. An appraisal of study relevance as well as design and conduct gaps are reported in Tables 5 and 6.

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 (ie, 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 3. 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 <i>BRAF</i> V600E or V600K variants: <ul style="list-style-type: none"> • 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 | 23 countries including | 124 | 2012-2015 | • Adults with completely resected stage IIC, IIIA, or IIIB | <ul style="list-style-type: none"> • Cohort 1: n=157 • Cohort 2: n=93 | <ul style="list-style-type: none"> • Cohort 1: n=157 • Cohort 2: n=91 |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

| Study; Trial | Countries | Sites | Dates | Participants | Interventions |
|---------------|-----------|-------|-------|--|--|
| (NCT01667419) | U.S. | | | (cohort 1) or stage IIIC (cohort 2) melanoma with <i>BRAF</i> V600E or V600K variants <ul style="list-style-type: none"> Cohort 1: <ul style="list-style-type: none"> Stage IIC: 9% Stage IIIA: 24% Stage IIIB: 68% Cohort 2: <ul style="list-style-type: none"> Stage IIIC: 100% | <ul style="list-style-type: none"> Vemurafenib (960 mg bid) for 12 mo Matching placebo |

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

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

| Study | Median Recurrence-Free Survival, mo | | Distant Metastasis % Over Study Period | Death % Over Study Period | SAEs |
|---|---|--|--|--------------------------------|------------------------|
| | Recurrence or Death | | | | |
| 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 |
| 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 5. 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 | | |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

| | |
|-------------------|---|
| | 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 6. 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 (ie, 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

GLIOMA

When 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 *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.

Interventions

The intervention of interest 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 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.

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 7. 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 <i>BRAF</i> activation (<i>KIAA-BRAF</i> fusion or <i>BRAF</i> -activating variant including <i>BRAF</i> 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; <i>BRAF</i> 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 | Adults with | 54; <i>BRAF</i> status | Bevacizumab 5 mg/kg | 6-mo, 20.4% | 5.6 (4.7 to 8.2) |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

| Study | Populations | N | Treatment(s) | Results (95% CI), mo | |
|-------------------------|---|-------------------------------------|--|-------------------------------|---------------------|
| (2013) | recurrent GBM | not reported | per 2 wk plus sorafenib 200 mg qd or bid | | |
| Zustovich et al (2013) | Adults with recurrent GBM | 53; <i>BRAF</i> 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 (2013) | High-grade glioma (primary or recurrent) with at least 2 wk of RT | 18; <i>BRAF</i> status not reported | Sorafenib 200-400 mg bid plus: <ul style="list-style-type: none"> • Primary disease, TMZ 75 mg/m² per day and 60-Gy RT • Recurrent disease, 35 Gy in 10 fractions | | 18 (6 to undefined) |
| Peereboom et al (2013) | Adults with recurrent or progressive GBM | 56; <i>BRAF</i> 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; <i>BRAF</i> 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; <i>BRAF</i> 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. Ongoing early-phase studies evaluating BRAF and MEK inhibitors are listed in Table 8.

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)

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

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 unresectable 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 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 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Targeted Therapy", 2.04.77, 06:2018.
2. American Cancer Society. Cancer Facts & Figures 2017. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf>. Accessed June 2, 2017.
3. Gogas HJ, Kirkwood JM, Sondak VK. Chemotherapy for metastatic melanoma: time for a change? *Cancer*. Feb 1 2007;109(3):455-464. PMID 17200963
4. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. Aug 2015;16(8):908-918. PMID 26115796
5. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *J Clin Oncol*. Apr 01 2015;33(10):1191-1196. PMID 25713437
6. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. Jan 22 2015;372(4):320-330. PMID 25399552
7. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. Jun 30 2011;364(26):2517-2526. PMID 21639810
8. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. Apr 2015;16(4):375-384. PMID 25795410
9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed May 17, 2017.
10. Vultur A, Villanueva J, Herlyn M. Targeting BRAF in advanced melanoma: a first step toward manageable disease. *Clin Cancer Res*. Apr 1 2011;17(7):1658-1663. PMID 21447722
11. Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature*. Sep 30 2010;467(7315):596-599. PMID 20823850
12. Sondergaard JN, Nazarian R, Wang Q, et al. Differential sensitivity of melanoma cell lines with BRAFV600E mutation to the specific Raf inhibitor PLX4032. *J Transl Med*. 2010;8:39. PMID 20406486
13. Joseph EW, Pratilas CA, Poulikakos PI, et al. The RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a V600E BRAF-selective manner. *Proc Natl Acad Sci U S A*. Aug 17 2010;107(33):14903-14908. PMID 20668238
14. Yang H, Higgins B, Kolinsky K, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. *Cancer Res*. Jul 1 2010;70(13):5518-5527. PMID 20551065
15. King AJ, Patrick DR, Batorsky RS, et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. *Cancer Res*. Dec 1 2006;66(23):11100-11105. PMID 17145850
16. Takle AK, Brown MJ, Davies S, et al. The identification of potent and selective imidazole-based inhibitors of B-Raf kinase. *Bioorg Med Chem Lett*. Jan 15 2006;16(2):378-381. PMID 16260133
17. GlaxoSmithKline. Tafenlar (dabrafenib) capsules prescribing information, January 2014. <http://www.tafenlar.com/>. Accessed August 13, 2015.
18. Rubinstein JC, Sznol M, Pavlick AC, et al. Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to the specific BRAF inhibitor PLX4032. *J Transl Med*. 2010;8:67. PMID 20630094
19. GlaxoSmithKline. Mekinist (trametinib) tablets prescribing information, January 2014. <http://www.mekinist.com/>. Accessed August 13, 2015.
20. Genentech, Inc. Cotellic(r) (cobimetinib) highlights of prescribing information, May 2016. https://www.gene.com/download/pdf/cotellic_prescribing.pdf. Accessed May 24, 2017.
21. Central Brain Tumor Registry of the United States. 2016 CBTRUS Fact Sheet. n.d.; <http://www.cbtrus.org/factsheet/factsheet.html>.
22. Louis DN, Ohgaki H, Wiestler HOD, et al. WHO Classification of Tumours of the Central Nervous System. Revised. 4th ed. Lyon: WHO Press; 2016.
23. Chien LN, Gittleman H, Ostrom QT, et al. Comparative brain and central nervous system tumor incidence and survival between the United States and Taiwan based on population-based registry. *Front Public Health*. 2016;4:151. PMID 27493936
24. Dougherty MJ, Santi M, Brose MS, et al. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. *Neuro Oncol*. Jul 2010;12(7):621-630. PMID 20156809

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

25. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* Mar 2011;121(3):397-405. PMID 21274720
26. Myung JK, Cho H, Park CK, et al. Analysis of the BRAF(V600E) mutation in central nervous system tumors. *Transl Oncol.* Dec 2012;5(6):430-436. PMID 23323158
27. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet.* Jun 2013;45(6):602-612. PMID 23583981
28. Horbinski C, Nikiforova MN, Hagenkord JM, et al. Interplay among BRAF, p16, p53, and MIB1 in pediatric low-grade gliomas. *Neuro Oncol.* Jun 2012;14(6):777-789. PMID 22492957
29. Forsheew T, Tatevossian RG, Lawson AR, et al. Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. *J Pathol.* Jun 2009;218(2):172-181. PMID 19373855
30. Behling F, Barrantes-Freer A, Skardelly M, et al. Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. *Diagn Pathol.* Jun 27 2016;11(1):55. PMID 27350555
31. Dummer R, Goldinger SM, Turtzchi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer.* Feb 2014;50(3):611-621. PMID 24295639
32. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* Nov 2012;13(11):1087-1095. PMID 23051966
33. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). 2017 (May 3); <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>. Accessed June 5, 2017.
34. Genentech, Inc. Zelboraf® (vemurafenib) tablet prescribing information, March 2014. <http://www.zelboraf.com/>. Accessed August 13, 2015.
35. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Special Report. Companion diagnostics: Example of BRAF testing to select patients with melanoma for BRAF kinase inhibitors. TEC Assesment Program. 2011;Volume 26:Tab 7.
36. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med.* Jan 2009;11(1):3-14. PMID 18813139
37. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* Jun 30 2011;364(26):2507-2516. PMID 21639808
38. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* Feb 23 2012;366(8):707-714. PMID 22356324
39. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med.* Aug 26 2010;363(9):809-819. PMID 20818844
40. Luke JJ, Hodi FS. Vemurafenib and BRAF inhibition: a new class of treatment for metastatic melanoma. *Clin Cancer Res.* Jan 1 2012;18(1):9-14. PMID 22083257
41. Halait H, Demartin K, Shah S, et al. Analytical performance of a real-time PCR-based assay for V600 mutations in the BRAF gene, used as the companion diagnostic test for the novel BRAF inhibitor vemurafenib in metastatic melanoma. *Diagn Mol Pathol.* Mar 2012;21(1):1-8. PMID 22306669
42. Anderson S, Bloom KJ, Vallera DU, et al. Multisite analytic performance studies of a real-time polymerase chain reaction assay for the detection of BRAF V600E mutations in formalin-fixed, paraffin-embedded tissue specimens of malignant melanoma. *Arch Pathol Lab Med.* 2012/11/01 2012;136(11):1385-1391. PMID
43. Food and Drug Administration. THxID™-BRAF kit for use on the ABI 7500 Fast Dx Real-Time PCR Instrument - P120014. BioMérieux labeling. 2013; <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p120014>. Accessed August 13, 2015.
44. Anwar MA, Murad F, Dawson E, et al. Immunohistochemistry as a reliable method for detection of BRAF-V600E mutation in melanoma: a systematic review and meta-analysis of current published literature. *J Surg Res.* Jun 15 2016;203(2):407-415. PMID 27363650
45. O'Brien O, Lyons T, Murphy S, et al. BRAF V600 mutation detection in melanoma: a comparison of two laboratory testing methods. *J Clin Pathol.* Apr 19 2017. PMID 28424234
46. Huang WK, Kuo TT, Wu CE, et al. A comparison of immunohistochemical and molecular methods used for analyzing the BRAF V600E gene mutation in malignant melanoma in Taiwan. *Asia Pac J Clin Oncol.* Dec 2016;12(4):403-408. PMID 27488807

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

47. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. Jul 28 2012;380(9839):358-365. PMID 22735384
48. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114. PMID 22663011
49. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. Aug 1 2015;386(9992):444-451. PMID 26037941
50. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. Jan 1 2015;372(1):30-39. PMID 25399551
51. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. Sep 2016;17(9):1248-1260. PMID 27480103
52. Food and Drug Administration (FDA). FDA Summary of Safety and Effectiveness Data (SSED): THxID™ BRAF Kit for use on the ABI 7500 Fast Dx Real-Time PCR Instrument. 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120014b.pdf.
53. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. Nov 13 2014;371(20):1877-1888. PMID 25265492
54. Amdahl J, Chen L, Delea TE. Network meta-analysis of progression-free survival and overall survival in first-line treatment of BRAF mutation-positive metastatic melanoma. *Oncol Ther*. 2016;4(2):239-256. PMID 28261653
55. Devji T, Levine O, Neupane B, et al. Systemic therapy for previously untreated advanced BRAF-mutated melanoma: a systematic review and network meta-analysis of randomized clinical trials. *JAMA Oncol*. Mar 01 2017;3(3):366-373. PMID 27787543
56. Pasquali S, Chiarion-Sileni V, Rossi CR, et al. Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: A network meta-analysis. *Cancer Treat Rev*. Mar 2017;54:34-42. PMID 28189914
57. Karajannis MA, Legault G, Fisher MJ, et al. Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. *Neuro Oncol*. Oct 2014;16(10):1408-1416. PMID 24803676
58. Hottinger AF, Aissa AB, Espeli V, et al. Phase I study of sorafenib combined with radiation therapy and temozolomide as first-line treatment of high-grade glioma. *Br J Cancer*. May 27 2014;110(11):2655-2661. PMID 24786603
59. Galanis E, Anderson SK, Lafky JM, et al. Phase II study of bevacizumab in combination with sorafenib in recurrent glioblastoma (N0776): a north central cancer treatment group trial. *Clin Cancer Res*. Sep 01 2013;19(17):4816-4823. PMID 23833308
60. Zustovich F, Landi L, Lombardi G, et al. Sorafenib plus daily low-dose temozolomide for relapsed glioblastoma: a phase II study. *Anticancer Res*. Aug 2013;33(8):3487-3494. PMID 23898124
61. Den RB, Kamrava M, Sheng Z, et al. A phase I study of the combination of sorafenib with temozolomide and radiation therapy for the treatment of primary and recurrent high-grade gliomas. *Int J Radiat Oncol Biol Phys*. Feb 01 2013;85(2):321-328. PMID 22687197
62. Peereboom DM, Ahluwalia MS, Ye X, et al. NABTT 0502: a phase II and pharmacokinetic study of erlotinib and sorafenib for patients with progressive or recurrent glioblastoma multiforme. *Neuro Oncol*. Apr 2013;15(4):490-496. PMID 23328813
63. Lee EQ, Kuhn J, Lamborn KR, et al. Phase I/II study of sorafenib in combination with temsirolimus for recurrent glioblastoma or gliosarcoma: North American Brain Tumor Consortium study 05-02. *Neuro Oncol*. Dec 2012;14(12):1511-1518. PMID 23099651
64. Hainsworth JD, Ervin T, Friedman E, et al. Concurrent radiotherapy and temozolomide followed by temozolomide and sorafenib in the first-line treatment of patients with glioblastoma multiforme. *Cancer*. Aug 01 2010;116(15):3663-3669. PMID 20564147
65. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. Aug 20 2015;373(8):726-736. PMID 26287849
66. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1.2016. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 24, 2017.
67. Food and Drug Administration. SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED): FoundationOne CDx™. 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. Accessed April 26, 2018.
68. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. *Ann Oncol*. Oct 1 2017;28(10):2581-2587. PMID 28961848
69. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. Aug 1 2015;386(9992):444-451. PMID 26037941

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

70. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* May 2018;19(5):603-615. PMID 29573941
71. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med.* Nov 9 2017;377(19):1813-1823. PMID 28891408
72. Maio M, Lewis K, Demidov L, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol.* Apr 2018;19(4):510-520. PMID 29477665

Policy History

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

11/03/2011 Medical Policy Committee review

11/16/2011 Medical Policy Implementation Committee approval. New policy.

11/01/2012 Medical Policy Committee review

11/28/2012 Medical Policy Implementation Committee approval. "Targeted" added to the title. Eligible for coverage statement modified to read "FDA-approved BRAF inhibitors" in place of "vemurafenib"

12/12/2013 Medical Policy Committee review

12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2015 Coding Update

01/08/2015 Medical Policy Committee review

01/21/2015 Medical Policy Implementation Committee approval. New policy.

01/07/2016 Medical Policy Committee review

01/22/2016 Medical Policy Implementation Committee approval. No change to coverage.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

01/05/2017 Medical Policy Committee review

01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.

10/05/2017 Medical Policy Committee review

10/18/2017 Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. Policy statements regarding BRAF testing in melanoma unchanged. 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".

08/09/2018 Medical Policy Committee review

08/15/2018 Medical Policy Implementation Committee approval. New policy statement added stating BRAF testing in resected, stage III melanoma is eligible for coverage. "Mutation" changed to "variant" in policy title.

Next Scheduled Review Date: 08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
 Original Effective Date: 11/16/2011
 Current Effective Date: 08/15/2018

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|------------------|--------------------------|
| CPT | 81210 |
| HCPCS | No codes |
| ICD-10 Diagnosis | C43.0-C43.9, D03.0-D03.9 |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320

Original Effective Date: 11/16/2011

Current Effective Date: 08/15/2018

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.