Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma AHS-M2029

Description of Procedure or Service

BRAF (V-raf murine sarcoma viral oncogene homolog B1) is a serine-threonine protein kinase involved in cell survival, proliferation, and differentiation (H. Davies et al., 2002; Tatsuno et al., 2016). The most common missense mutation of \textit{BRAF} (mainly V600E) contributes to the incidence of various cancers, including melanoma (Flaherty et al., 2012).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing and genetic expression profiling in patients with cutaneous melanoma when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma is covered

1. Testing of tumor tissue for \textit{BRAF} V600 and \textit{KIT} mutation analysis is considered \textit{medically necessary} for individuals with unresectable or metastatic melanoma (stage IV), prior to initiation of molecular targeted treatment.

   Note: Mutation testing on the metastatic lesion is preferred, if possible.

2. Testing of tumor tissue for \textit{BRAF} V600 mutation analysis is considered \textit{medically necessary} for individuals who have resected stage III melanoma.

When Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma is not covered

Genetic expression profiling testing for cutaneous melanoma is considered investigational.

Testing for \textit{BRAF} V600, \textit{KIT} and other mutations in other forms or stages of melanoma is considered investigational.
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Note: For testing of 5 or more genes for an affected individual with cutaneous melanoma, please refer to AHS-M2109 Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy.

Policy Guidelines

The incidence of melanoma in the United States appears to be increasing more rapidly than any other malignancy. The lifetime risk for the general population of developing melanoma is 1 in 55 (Institute, 2016) and that risk has increased approximately 2% annually since 1960 (Rashid & Zager, 2015).

**New cases & deaths of Melanoma per 100,000 persons** (SEER 18 2009-2013)

The number of new cases of melanoma of the skin was 21.8 per 100,000 men and women per year, 4.5% of all new cancer cases. The number of deaths was 2.7 per 100,000 men and women per year, 1.7% of all cancer deaths in US in 2016 (Institute, 2016).

Melanoma is particularly lethal and aggressive, with the ability to metastasize to any organ (Leong et al., 2011). Cutaneous tumors as little as 1 mm in thickness are capable of lymph node metastasis (Stage III) which results in a significant decrease in the 5-year survival rate from 90% to 56% (Yee et al., 2005). Spread beyond the lymph nodes (Stage IV) results in an even more dramatic decrease in 5-year survival to 15%. (Grossmann, Grossmann, & Wallander, 2012)

Historically, systemic therapy for metastatic melanoma provided very low response rates and little to no benefit in overall survival (Atkins, Kunkel, Sznol, & Rosenberg, 2000; Tsao, Atkins, & Sober, 2004). Recently, the immune-boosting anti-CTLA-4 antibody ipilimumab (Hodi et al., 2010) and testing and development of small molecule kinase (KIT and BRAF) inhibitors have yielded improvements in long-term survival (M. A. Davies & Gershenwald, 2011; Ribas & Flaherty, 2011; Woodman & Davies, 2010).
Activating *BRAF* mutations occur in approximately half of cutaneous melanomas (H. Davies et al., 2002; Hocker & Tsao, 2007). *BRAF* is a member of the RAF family of protein serine/threonine kinases (ARAF, BRAF, CRAF) which is activated by Ras proteins during intracellular signaling cascades. Mutations in *BRAF* appear to be the most common genetic alteration in melanoma (Hocker & Tsao, 2007) and occur more frequently in melanoma than lung, colon, and ovarian carcinoma (Grossmann et al., 2012). More than 30 mutations of the *BRAF* gene associated with human cancers have been identified (Siroy et al., 2015). In 90% of the cases, thymine is substituted with adenine at nucleotide 1799. This leads to valine (V) being substituted for by glutamate (E) at codon 600 (now referred to as V600E) in the kinase domain (Tan et al., 2008). Importantly, *BRAF* activating mutations occur in up to 80% of benign nevi and, therefore, cannot be used to distinguish benign from malignant melanocytic lesions (Grossmann et al., 2012; Poynter et al., 2006).

**Table 1.** Frequency of melanoma subtypes with activating genetic alterations in *BRAF* and *KIT* (Grossmann et al., 2012)

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Cutaneous −CSD</th>
<th>Cutaneous + CSD</th>
<th>ALM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRAF</em>&lt;sub&gt;g&lt;/sub&gt; mutation</td>
<td>53%</td>
<td>8–11%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td><em>KIT</em> mutation; amplification</td>
<td>0</td>
<td>17%</td>
<td>11–38%;</td>
<td>6–19%;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19–27%</td>
<td>20–33%</td>
</tr>
</tbody>
</table>
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Despite the high frequency in nevi, the role of BRAF mutation in oncogenesis is well established (M. A. Davies & Gershenwald, 2011) and has been confirmed in clinical trials (Flaherty et al., 2010). The remarkable efficacy of BRAF inhibitors led to the accelerated approval of vemurafenib for unresectable and metastatic melanoma. Importantly, BRAF mutation testing is warranted for determining therapeutic eligibility as selective BRAF inhibitors pose significant risk of cutaneous squamous cell carcinoma and have the potential to increase disease progression in BRAF wild type (mutation negative) tumors (Grossmann et al., 2012).

A variety of methods are currently utilized for BRAF and KIT mutational analysis in melanoma, which has resulted in no standardized procedures for testing. However, labs have been reluctant to switch BRAF platforms to accommodate one specific drug for one disease (Grossmann et al., 2012). However, a recent study found good overall compliance of labs with CAP (Cree, 2014) and NCCN guidelines for molecular diagnosis of tumors (Volmar, Idowu, Souers, & Nakhleh, 2015) despite not using the specific FDA-approved test.

Table 2. Molecular Testing Adherence to NCCN Guidelines (Volmar et al., 2015)

<table>
<thead>
<tr>
<th>Retrospective study (lung, colorectal, melanoma)</th>
<th>10th</th>
<th>25th</th>
<th>Median</th>
<th>75th</th>
<th>90th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of tests that strictly meet the guideline</td>
<td>26</td>
<td>32.6</td>
<td>64.7</td>
<td>70.9</td>
<td>82.7</td>
</tr>
<tr>
<td>Percentage of tests that at least loosely meet the guideline</td>
<td>26</td>
<td>57.4</td>
<td>96.7</td>
<td>95.1</td>
<td>98.9</td>
</tr>
<tr>
<td>Prospective study (all case types)</td>
<td>72</td>
<td>20.0</td>
<td>31.4</td>
<td>53.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Percentage of tests that strictly meet the guideline</td>
<td>23</td>
<td>75.0</td>
<td>87.0</td>
<td>94.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Percentage of tests that at least loosely meet the guideline</td>
<td>23</td>
<td>75.0</td>
<td>87.0</td>
<td>94.3</td>
<td>100.0</td>
</tr>
</tbody>
</table>

BRAF analysis is accepted medical practice for patients with unresectable, metastatic stage IV melanoma (NCCN, 2018). Recent randomized controlled trials (RCTs), however, have indicated the benefits of expanding BRAF analysis. A study published in The Lancet Oncology in 2018 by Amaria and colleagues compared standard of care in patients with high-risk, surgically resectable melanoma (stage III or IV) to similar patients receiving a regimen of a neoadjuvant plus adjuvant dabrafenib and trametinib. All patients had to be of confirmed BRAF V600E or BRAF V600K status to participate in either the control or experimental groups. In the follow-up (median of 18.6 months), 10/14 (or 71%) of patients in the experimental group remained event-free (i.e. alive without disease progression) whereas 0/7 (0%) of the control group receiving standard of care remained event-free. The authors conclude, “Neoadjuvant plus adjuvant dabrafenib and trametinib significantly improved event-free survival versus standard of care in patients with high-risk, surgically resectable, clinical stage III-IV melanoma (Amaria et al., 2018).”

Another study published in 2017 researched the use of perioperative BRAF inhibitors on patients with stage III melanoma. All patients had to be confirmed BRAF V600E to participate in the study. Of the thirteen patients, twelve “patients showed a marked clinical responsiveness to medical treatment, enabling a macroscopically successful resection in all cases”; moreover, “at a median follow up of 20 months, 10 patients remain free of disease.” Only one patient died prior to surgery in this study. The authors conclude, “Perioperative treatment with BRAF inhibiting agents in BRAFV600E mutated Stage III melanoma patients facilitates surgical resection and affords satisfactory disease free (sic) survival (Zippel et al., 2017).”

State and Federal Regulations, as applicable

The FDA-approvals for all of the BRAF-targeted therapies include the requirement that BRAF mutation testing be performed by an FDA-approved test.
On August 17, 2011 the U.S. Food and Drug Administration (FDA) announced the approval of Zelboraf (vemurafenib) for unresectable or metastatic melanoma with oncogenic BRAF mutation (V600E). The Cobas® 4800 BRAF V600 Mutation Test was approved as the companion diagnostic for vemurafenib (Bollag et al., 2012).

Dabrafenib was FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. Dabrafenib is specifically not indicated for the treatment of patients with wild-type BRAF melanoma (Tafinlar (dabrafenib), Jan 2014).

Trametinib was FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy (GlaxoSmithKline. Mekinist Aug 2014).

The companion diagnostic test coapproved for both dabrafenib and trametinib is the THxID™ BRAF Kit manufactured by bioMérieux. The kit is intended “as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for treatment with trametinib” (Genentech, Inc. Zelboraf® March, 2014).

The FDA approved the use of the Oncomine Dx target test NGS panel for somatic or germline variants, which includes the BRAF V600E mutation for consideration with dabrafenib therapy as one of the gene variants (Life Technologies Corporation, approved in June 2017).

The FDA approved the FoundationOne CDx NGS panel in November 2017, which does include both the V600E and V600K mutation for possible dabrafenib or vemurafenib therapy. (Foundation Medicine, Inc.).

Tests Available:
- **BRAF V600E** by real-time PCR
- **BRAF (V600E) mutation only by Sanger sequencing**
- **BRAF full gene sequence analysis**
- **BRAF next generation sequencing**

Available Tests and Analytical Sensitivities:
- The **BRAF V600E** by real-time PCR test uses a TaqMan® Mutation Detection Assay to detect the V600E mutation in exon 15 of **BRAF** in tumor (somatic) cells. The sensitivity of the TaqMan assay is ~0.1% mutant DNA in a wild-type background. Poor DNA quality, insufficient DNA quantity or the presence of PCR inhibitors can result in uninterpretable or (rarely) inaccurate results.
- The **BRAF (V600E) mutation only** by Sanger sequencing uses a DNA-based PCR-sequencing assay to detect the V600E in exon 15 of **BRAF**. The limit of detection for Sanger sequencing is >20% mutant DNA in a wild-type background.
- The **BRAF full gene sequence analysis** test uses a DNA-based PCR-sequencing assay to detect point mutations in the coding sequence and intron/exon boundaries of the **BRAF** gene. The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Rare variants at primer binding sites may lead to erroneous results. The limit of detection for Sanger sequencing is >20% mutant DNA in a wild-type background.
- The **BRAF NGS with TruSeq** had sensitivity of over 99%. (Froyen et al., 2016)

Guidelines and Recommendations


The NCCN Melanoma Panel strongly recommends testing for and reporting the presence or absence of **BRAF** and **KIT** gene mutations that may impact treatment options in patients with metastatic melanoma (stage IV patients). This testing is only recommended for patients with advanced disease for whom molecular targeted therapies could be beneficial. In addition, “mutational analysis for **BRAF** or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma who are otherwise no evidence of disease (NED) in status, unless required to guide systemic therapy or consideration of
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clinical trials.” The panel also states, “while there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low versus high risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanomas (before or following sentinel lymph node biopsy [SLNB]) is not recommended outside of a clinical study (trial).” It should be noted that as of 10/25/2018, the NCCN updated the status of the melanoma guidelines as “Discussion update in progress” (NCCN, 2018).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0089U, 0090U 81210, 81272, 81273

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: BRAF Genetic Testing in Patients with Melanoma


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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

Policy Implementation/Update Information

For Policy Titled: BRAF Genetic Testing in Patients with Melanoma

1/1/2019 New policy developed. BCBSNC will provide coverage for BRAF genetic testing in patients with melanoma when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

11/12/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

For Policy Titled: Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma

2/11/20 Reviewed by Avalon Q4 2019 CAB. Under “When Not Covered” section added statement: Genetic expression profiling testing for cutaneous melanoma is considered investigational. Added Note: For testing of 5 or more genes for an affected individual with cutaneous melanoma, please refer to AHS-M2109 Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy. Under Billing/Coding section: Deleted CPT codes 81445, 81450, 81455 and added PLA codes: 0089U and 0090U. Policy Title changed from: BRAF Genetic Testing in Patients with Melanoma to: Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma. Medical Director review 1/2020. (lpr)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.