BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Targeted Therapy

<table>
<thead>
<tr>
<th>Type:</th>
<th>Medical Necessity and Investigational / Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Specific Section:</td>
<td>Laboratory/Pathology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Original Policy Date:</th>
<th>July 6, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Date:</td>
<td>April 4, 2014</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Description

V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors are drugs designed to target a somatic mutation in the BRAF gene of patients with advanced melanoma. The BRAF gene codes for a kinase component in the RAF/MEK/ERK signal transduction phosphorylation
cascade. The mutated version of the BRAF kinase results in constitutive activity, believed to be actively involved in oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to significantly retard tumor growth and may improve patient survival.

See related Blue Shield Medical Policy when BRAF gene mutation testing is used for other indications:

- Genetic Testing for Colorectal Cancer

**Policy**

Testing for the BRAF<sup>V600</sup> mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered **medically necessary** in order to select patients for treatment with FDA-approved BRAF inhibitors (See Policy Guidelines).

Testing for the BRAF<sup>V600</sup> mutation for all other patients with melanoma, including but not limited to, use in patients with lesser stage melanoma, is considered **investigational**.

**Policy Guideline**

**U.S. Food and Drug Administration (FDA)-Approved BRAF Inhibitors**

Currently, only the following drugs are FDA-approved specifically for the treatment of advanced BRAF-mutated melanoma:

- Vemurafenib (Zelboraf®)
- Dabrafenib (Tafinlar®)
- Trametinib (Mekinist™)

**U.S. FDA-Approved Companion Diagnostic Testing Kits for BRAF Mutation Testing**

There are FDA-approved BRAF testing kits intended to be used to select patients for treatment with vemurafenib and with dabrafenib and trametinib. There are also commercial labs that perform BRAF testing using non-FDA approved testing. The full prescribing information states that confirmation of the BRAF<sup>V600E</sup> mutation using an FDA-approved test is required for selection of patients appropriate for therapy. The intent of the FDA-approval of these testing kits is to minimize the potential for inappropriate treatment based on an inaccurate test.

The companion diagnostic tests that are FDA approved include:

- For vemurafenib (Zelboraf®): cobas® 4800 BRAF V600 Mutation Test manufactured by Roche (Pleasanton, CA)
- For both dabrafenib (Tafinlar®) and trametinib (Mekinist™): THxID™ BRAF test manufactured by bioMérieux (Durham, NC)

**Other Information**

The Phase III clinical trial of vemurafenib selected all patients with a BRAF<sup>V600</sup> mutation using the FDA-approved test. The majority of these mutations were BRAF<sup>V600E</sup> mutations, and a small number (19/675, 2.8%) were BRAF<sup>V600K</sup> mutations. The authors stated that patients with the
BRAF\textsuperscript{V600K} also appeared to respond to vemurafenib, but no formal subgroup analysis was performed. Therefore, the results of the trial refer primarily to patients with the $BRAF\textsuperscript{V600E}$ mutation. The efficacy of vemurafenib for patients with other mutations, including $BRAF\textsuperscript{V600K}$, is less certain.

A Phase II, single-arm study of dabrafenib enrolled 172 patients with either BRAF\textsuperscript{V600E} – or BRAF\textsuperscript{V600K} -mutated melanoma with brain metastasis. Overall intracranial response was limited to patients with the BRAF\textsuperscript{V600E} mutation and was negligible in patients with the BRAF\textsuperscript{V600K} mutation.

**Coding**

There is a specific CPT code for BRAF Gene Mutation Testing* when used to select BRAF Inhibitor Targeted Therapy:

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

The following unlisted molecular pathology procedure code may be used to describe gene analysis of V600K variant:

- 81479: Unlisted molecular pathology procedure [when specified as gene analysis of V600K variant]*

*Note: BRAF gene mutation testing is also discussed in related Blue Shield Medical Policy: Genetic Testing for Colorectal Cancer for other indications.

**Melanoma Staging (American Cancer Society, 2013)**

The following is based on the American Joint Committee on Cancer (AJCC) TNM System:

- T stands for tumor (how far it has grown within the skin and other factors). The T category numbers (from 0 to 4) are based on the tumor thickness. It may also be assigned a small letter "a" or "b" based on ulceration and mitotic rate
- N stands for spread to nearby lymph nodes. The N category numbers (from 0 to 3) are based on whether the melanoma cells have spread to the lymph nodes. It may also be assigned an "a" or "b" or "c"
- M stands for whether the melanoma has metastasized (spread) to distant organs which organs it has reached, and on blood levels of LDH.

There are two types of staging for melanoma:

- Clinical staging is based on what is found on physical exam, biopsy/removal of the main melanoma, and any imaging tests that are done.
- Pathologic staging uses all of this information, plus what is found during biopsies of lymph nodes or other organs if they are done.

The pathologic stage (determined after the lymph node biopsy) may actually be higher than the clinical stage (determined before the lymph node biopsy) if the biopsy finds cancer in new areas.
If the pathologic stage is available, it gives a more accurate picture of the extent of the cancer, but in many cases lymph node biopsies are not needed.

**Stage IIIC (one of the following applies):**

- T1b to T4b, N1b or N2b, M0: The melanoma can be of any thickness and is ulcerated. It has spread to 1 to 3 lymph nodes near the affected skin area. The nodes are enlarged because of the melanoma. There is no distant spread.
- T1b to T4b, N2c, M0: The melanoma can be of any thickness and is ulcerated. It has spread to small areas of nearby skin or lymphatic channels around the original tumor, but the nodes do not contain melanoma. There is no distant spread.
- Any T, N3, M0: The melanoma can be of any thickness and may or may not be ulcerated. It has spread to 4 or more nearby lymph nodes, OR to nearby lymph nodes that are clumped together, OR it has spread to nearby skin or lymphatic channels around the original tumor and to nearby lymph nodes. The nodes are enlarged because of the melanoma. There is no distant spread.

**Stage IV**

- Any T, any N, M1 (a, b, or c): The melanoma has spread beyond the original area of skin and nearby lymph nodes to other organs such as the lung, liver, or brain, or to distant areas of the skin, subcutaneous, tissue, or distant lymph nodes. Neither spread to nearby lymph nodes nor thickness is considered in this stage, but typically the melanoma is thick and has also spread to the lymph nodes.

**Documentation Required for Clinical Review**

- History and physical and/or consultation notes including:
  - Differential diagnosis, prognosis, and cancer staging
  - Specific FDA-approved test requested (e.g., cobas 4800 BRAF V600 Mutation Test)
  - Clinical justification/reason for testing
  - Treatment plan
- Laboratory and pathology reports (including cancer staging and FDA-approved BRAF V600 mutation test results)

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.