GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Melanoma is a form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Description: (cont.)

Metastasis is the spread of cancer from one part of the body to another. The metastatic tumor contains cells that are like those in the original (primary) tumor.

About half of all melanomas have variants in the BRAF gene. These changes cause the gene to make an altered BRAF protein that signals the melanoma cells to grow and divide.

Glioma is a broad category type of tumor that occurs in the brain and the spinal cord. Types of glioma include astrocytomas, ependymomas, and oligodendrogliomas.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib (Zelboraf®; Roche/Genentech and Plexxikon)</td>
<td>• 2011: treatment of patients with unresectable or metastatic melanoma with <em>BRAF</em> V600 variants</td>
<td>• 2011: cobas® 4800 BRAF V600 Mutation Test (Roche)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
</tr>
</tbody>
</table>
| Dabrafenib (Tafinlar®; GlaxoSmithKline) | • 2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variants  
• 2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants  
• 2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants | • 2013: THxID™ BRAF kit (bioMérieux)                                          |
|                                  |                                                                             | • 2017: FoundationOne CDx™ (Foundation Medicine)                              |
| Trametinib (Mekinist™; GlaxoSmithKline) | • 2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants  
• 2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants  
• 2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants | • 2013: THxID™ BRAF kit (bioMérieux)                                          |
|                                  |                                                                             | • 2017: FoundationOne CDx™ (Foundation Medicine)                              |
| Cobimetinib (Cotellic®; Genentech) | • 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variants | • 2017: FoundationOne CDx™ (Foundation Medicine)                              |

FDA; product code: OWD
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Description: (cont.)

Definitions:

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

Gene:
A hereditary unit consisting of segments of DNA that occupies a specific location on chromosomes. Genes undergo mutation when their DNA sequence changes.

Genetic Counseling:
Instruction that provides interpretation of genetic tests and information about courses of action that are available for the care of an individual with a genetic disorder or for future family planning.

Affected Individual:
An individual displaying signs or symptoms characteristic of a suspected or specific inherited disorder.

Unaffected Individual:
An individual who displays no signs or symptoms characteristic of a suspected or specific inherited disorder.

Screening:
Genetic screening is the testing of an individual with no symptoms for a specific inherited disorder to determine if the individual carries an abnormal gene. Screening can be used to predict risk or potential risk for the individual or their offspring.

Criteria:

- Genetic testing and/or counseling of an unaffected individual, regardless of risk factors is considered screening and not eligible for coverage.

- Genetic testing and/or counseling of an affected individual to confirm a disease when confirmation of the diagnosis would not impact the care and/or management is considered not medically necessary and not eligible for coverage.

- Genetic testing and counseling for BRAF V600 variants in tumor tissue of affected individuals with unresectable or metastatic melanoma is considered medically necessary to select individuals for treatment with FDA-approved BRAF or MEK inhibitors.
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Criteria: (cont.)

- Genetic testing for BRAF V600 variants in in tumor tissue of individuals with resected stage III melanoma is considered **medically necessary** to select individuals for treatment with Food and Drug Administration-approved BRAF or MEK inhibitors.

- Repeat genetic testing is considered **medically necessary** only when indicated for monitoring of treatment response to medication.

- Genetic testing and counseling for BRAF V600 variants in glioma to select individuals for targeted treatment is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

- Genetic testing and counseling for BRAF V600 variants in melanoma for all other indications not previously listed or if above criteria not met is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Resources:

Literature reviewed 07/13/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 09/17/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

2. FDA. Zelboraf® (vemurafenib) 08/2015.
3. FDA. Tafinlar® (debrafenib mesylate) 11/2015.
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kweé atah nilinígíí Blue Cross Blue Shield of Arizona haada yít’éego bíina’ídilkidgo éi docdago Háida bií ánilíyee’ddíí t’áadoo te’é yina’ídilkidgo beeheaz’áanii hólo’o díí t’áa hazaad’ehjí háhá a’doowolgo bee ház’á doo báq’áh ílínígódíí. Áta’ halne’ígíí köjí bič’íí’ hodíilíní 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thống dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تتبع أسلحة بخصوص صحة، ففي الحرص على المساعدة والمعلومات Blue Cross Blue Shield of Arizona لم تأتي الحق في الحصول على المساعدة والموارد الضرورية بلغتك من دون اية تكلفة. للتحدث مع متجر اتصل ب 877-475-4799.
GENETIC TESTING FOR BRAF GENE VARIANT FOR TARGETED THERAPY IN MELANOMA OR GLIOMA (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyang wika ng walang gastos. Upang makasap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하에 편리로 사용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けること、情報を入手したりすることができるです。料金はかかりません。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: اگر شما یا کسی که شما به آن کمک می‌کنید، سوال‌هایی در مورد اطلاعاتی درباره گازوکسید را بپرسید، اطلاعات را در اختیار شما قرار دهنده، 877-475-4799 را می‌توانید تماس حاضری نمایید.

Assyrian: ناسیونال‌سی یا یکه کیشادا یا ناسیونال‌سی، بیل مارد دەکەیە، بەمەستەرەکەیە. بەمەستەرەکەیە، ناسیونال‌سی لە 877-475-4799دا ناسیونال‌سی لە 877-475-4799دا.

Serbo-Croatian: Ukoiko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodocem, nazovite 877-475-4799.

Thai: หากคุณหรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณจะได้รับความช่วยเหลือและข้อมูลในภาษาของคุณได้โดยไม่ค่าใช้จ่าย โปรดโทรหมายเลข โทร 877-475-4799.