GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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:

Specific, targetable oncogenic “driver” mutations have been identified in a subset of non-small cell lung cancers (NSCLCs). The first successful example of targeted therapy involved mutations in the epidermal growth factor receptor (EGFR) gene. Other oncogenic mutations in lung cancer have been investigated including the KRAS, ROS, RET, MET, BRAF and HER2 gene mutations.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Description: (cont.)

EGFR:
Mutations in the epidermal growth factor receptor (EGFR) gene can predict effective treatment of advanced non-small cell lung cancer (NSCLC) with tyrosine kinase inhibitors (TKIs) such as erlotinib (Tarceva®), gefitinib (Iressa®) or afatinib (Gilotrif™). EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Mutations in the EGFR gene (exons 18-24) – small deletions in exon 19 and a point mutation in exon 21 (L858R) appear to predict tumor response to tyrosine kinase inhibitors (TKIs). Tumors with an acquired exon 20 (T790M) substitution mutation appear to respond to osimertinib (Tagrisso™) following failure of TKI therapy. Genetic testing is performed to determine if an individual with advanced NSCLC should be considered for targeted therapy or if better suited for alternative therapies.

ALK:
ALK (anaplastic lymphoma kinase) is a tyrosine kinase that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement which leads to a fusion gene and expression of a protein with constitutive tyrosine kinase activity that has been demonstrated to play a role in controlling cell proliferation. The EML4-ALK fusion gene results from an inversion within the short arm of chromosome 2.

Current (2015) guidelines from the National Comprehensive Cancer Network recommend EGFR mutation and ALK rearrangement testing when performed in the workup of NSCLC in individuals with histologic subtypes adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified.

2014 guidelines issued jointly by the College of American Pathologists and partner Associations recommend:

1. EGFR mutation and ALK rearrangement testing in individuals with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history)
2. No EGFR mutation and ALK testing when an adenocarcinoma component is lacking; and
3. EGFR mutation and ALK testing when lung cancer specimens are limited (e.g., biopsy, cytology) and an adenocarcinoma component cannot be completely excluded. Clinical criteria (e.g., lack of smoking history, young age) may be useful to select a subset of these samples for testing.

KRAS:
KRAS mutations may be prognostic in NSCLC and may predict a lack of response to TKIs, but the impact of testing for these mutations on clinical management is unknown. Studies have not shown that KRAS mutations identify a population that may benefit from the use of anti-EGFR monoclonal antibodies. For the treatment of KRAS-mutated NSCLC, EGFR-TKIs and anti-EGFR monoclonal antibodies has been investigated as treatment options.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

**Description:** (cont.)

Other Mutations:
Other potentially targetable oncogenic mutations have been investigated in lung adenocarcinomas, including in the genes *ROS, RET, MET, BRAF, and HER2.*

**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.

*Gene Expression:*
The translation of the information encoded in a gene into messenger RNA (mRNA) which may or may not then be translated into a protein.

*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.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

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**.

**Epidermal Growth Factor Receptor (EGFR) Gene:**

- Genetic testing and/or counseling to determine EGFR mutation (small deletions in exon 19 and a point mutation in exon 21 [L858R]) is considered **medically necessary** to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa], or afatinib [Gilotrif]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

- Genetic testing and/or counseling of analysis for the T790M mutation in the gene for the EGFR receptor is considered **medically necessary** as a technique to predict treatment response to osimertinib (Tagrisso) in individuals who have progressed on or after EGFR TKI therapy.

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

- Genetic testing and/or counseling to determine EGFR mutation in NSCLC 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These indications include, **but are not limited to**:

- Individual with advanced NSCLC of squamous cell type
- Other EGFR mutations within exons 18 to 24
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Criteria: (cont.)

**Anaplastic Lymphoma Kinase (ALK) Gene:**

- Genetic testing and/or counseling to determine ALK gene somatic rearrangement mutations in an affected individual is considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®] or ceritinib [Zykadia™]) with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

- Genetic testing and/or counseling to determine ALK gene somatic rearrangement mutations 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

**Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Gene:**

- Genetic testing and/or counseling to determine KRAS gene mutation in an affected individual to predict non-response to anti-EGFR therapy with TKIs and for the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux®) in the treatment of non-small-cell lung cancer 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Criteria: (cont.)

Other Genes:

- Genetic testing and/or counseling for other gene mutations in an affected individual for targeted therapy in the treatment of non-small-cell lung cancer 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These genes include, but are not limited to:

- ROS
- RET
- MET
- BRAF
- HER2

Resources:

Literature reviewed 11/08/16. 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 02/05/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (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 kwe’é atah nílníígíí Blue Cross Blue Shield of Arizona haadá yit’éego bina’ídlíkíigo éí doodago Háída bijá aníllyeedíígi t’àado le’ é yína’ídlíkíigo beeház’ááníi hóó díí t’áa hazaadk’ehji háká a’dooowolgo bee haz’á doo báagh illínígóó. Ata’ haleh’e’ígí kojí bich’íí hodíílíih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插件項目的名稱 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 thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدك أسئلة بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أي تكلفة، للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay mga may katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makasuap 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 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 동역사와 얘기하기 위해서는 877-475-4799 로 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たり、情報を入手したりすることができます。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 او کمک می‌کنید، سوال در مورد اطلاعات به زبان خود را به موتور رایگان دریافت نمایید 877-475-4799. [گفتار تمامی تخمین]

Assyrian:

نام شما، می‌توانید به زبان خود، اطلاعات دریافت کنید. موبایل شما، 877-475-4799. [گفتار تمامی تخمین]

Serbo-Croatian: Ukoliko 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 prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคอมพิวเตอร์ของคุณมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถสอบถามข้อมูลและข้อมูลภาษาอื่น ๆ ของคุณได้โดยไม่เสียค่าใช้จ่าย ที่ 877-475-4799