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.

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

Description:

The identification of specific, targetable gene variants in a subset of non-small cell lung cancers (NSCLCs) has resulted in a reclassification of lung tumors. Genetic testing for variants in the anaplastic lymphoma kinase (ALK) gene, BRAF gene, epidermal growth factor receptor (EGFR) gene and ROS1 gene can predict tumor response and is used in clinical decision making for the treatment of NSCLC. Genetic testing of other gene variants in lung cancer has been investigated including the HER2, KRAS, MET and RET.

ALK (Anaplastic Lymphoma Kinase) Gene:
The ALK gene provides instructions for making a protein involved in cell growth. Changes in this gene can increase the growth and spread of NSCLC cells.

BRAF Gene:
The BRAF gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell’s nucleus. This protein is part of a signaling pathway known as the RAS/MAPK pathway which regulates the growth and division (proliferation) of cells. Changes in this gene can increase the growth and spread of NSCLC cells.

EGFR (Epidermal Growth Factor Receptor) Gene:
The EGFR gene provides instructions for making a protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor.

KRAS Gene:
The KRAS gene provides instructions for making a protein involved in cell signaling pathways that control cell growth, cell maturation and cell death. Changes in this gene can increase the growth and spread of cancer cells. Testing for changes in this gene has been investigated in the treatment of NSCLC.

ROS1 Gene:
The ROS1 gene provides instructions for making a gene involved in sending signals in cells and in cell growth. Changes in this gene can increase the growth and spread of NSCLC cells.

Other Genes:
Other potentially targetable gene variants have been investigated in lung adenocarcinomas, including the genes HER2, MET and RET.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Description: (cont.)

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Gene</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
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<tr>
<td>Afatinib (Gilotrif™)</td>
<td>EGFR</td>
<td>First line for individuals with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test</td>
<td>Therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit</td>
</tr>
<tr>
<td>Alectinib (Alecensa®)</td>
<td>ALK</td>
<td>Second line for individuals with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
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<tr>
<td>Brigatinib (Alunbrig™)</td>
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<td>Second line for individuals with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
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<tr>
<td>Ceritinib (Zykadia®)</td>
<td>ALK</td>
<td>Second line for individuals with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
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<tr>
<td>Crizotinib (Xalkori®)</td>
<td>ALK</td>
<td>First line for individuals with ALK-positive metastatic NSCLC as detected by FDA-approved test</td>
<td>Vysis ALK Break Apart FISH Probe Kit</td>
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<td>Crizotinib (Xalkori)</td>
<td>ROS1</td>
<td>First line for individuals with ROS1-positive metastatic NSCLC</td>
<td>Oncomine™ Dx Target Test</td>
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<tr>
<td>Dabrafenib (Tafinlar®) and trametinib (Mekinist®) combination</td>
<td>BRAF V600E</td>
<td>Used in combination as first line for individuals with metastatic NSCLC with BRAF V600E variant</td>
<td>Oncomine Dx Target Test</td>
</tr>
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</table>
| Erlotinib (Tarceva®) | EGFR | First line for individuals with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test  
Maintenance for individuals with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy  
Second line for individuals with locally advanced or metastatic NSCLC | Cobas® EGFR Mutation v2 Test (tissue or blood test) |
| Gefitinib (Iressa®) | EGFR | First line for individuals with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test  
Second line for individuals with locally advanced or metastatic NSCLC | Therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit  
Oncomine Dx Target Test |
| Osimertinib (Tagrisso®) | EGFR | Second line for individuals with metastatic NSCLC whose tumors have EGFR T790M mutations as detected by an FDA-approved test, who have not responded to EGFR-blocking therapy | Cobas® EGFR Mutation v2 Test (tissue or blood test) |
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (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.

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.

Anaplastic Lymphoma Kinase (ALK) Gene Testing:

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

- Genetic testing and/or counseling to determine ALK gene somatic rearrangement variants in an affected individual 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.

BRAF V600E Gene Testing:

- Genetic testing and/or counseling to determine BRAF V600E variant is considered medically necessary to predict treatment response to BRAF or MEK-inhibitor therapy e.g., dabrafenib (Tafinlar) and trametinib (Mekinist) in an affected individual with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Criteria: (cont.)

Epidermal Growth Factor Receptor (EGFR) Gene Testing:

- Genetic testing and/or counseling to determine EGFR variant (small deletions in exon 19 and a point variant 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 an affected individual with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

- Genetic testing and/or counseling for analysis to determine T790M variant in the gene for the EGFR receptor is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso) in an affected individual 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 in an affected individual 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.)

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

➢ Genetic testing and/or counseling to determine KRAS gene variant 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.

ROS1 Gene Testing:

➢ Genetic testing and counseling to determine ROS1 gene somatic rearrangement variants is considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in an affected individual with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Other Gene Testing:

➢ Genetic testing and/or counseling for other gene variants 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:

- HER2
- MET
- RET
GENETIC TESTING FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) (cont.)

Resources:

Literature reviewed 11/07/17. 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 níilíígíí Blue Cross Blue Shield of Arizona haada yít’éego bíná’ídlííkídgo éí doodago Háída bíjá aniýeeeldíí t’aadó le’é yína’ídlííkídgo beehaz’ááníí hóó díí t’áa hazaadk’éhí háká a’dooowolgo bee haz’á doo báa’át ilínígíí. Ata’ halne’éjíí koj’íí bích’įí hodiilinhíí 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 thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thợ dịch viễn, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدك أسئلة بأخصائص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أي تكلفة، للتحدث مع متبرع 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 tinutulungan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulung at impormasyon sa iyang wika ng walang gastos. Upang makausap ang isang tagasagot, 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 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 مهرگان دریافت نمایید 877-475-4799 تماس حاصل نمایید.

Assyrian: بی‌گناه بکاره‌گرینگ هرگونه سوالی از Blue Cross Blue Shield of Arizona نسبت به خیال‌های کمک و خدمات می‌دهند. تماس 877-475-4799 ضروری است.

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 หรือท่านที่รับประโยชน์ตามเกณฑ์ Blue Cross Blue Shield of Arizona คุณจะได้รับความสามารถในการขอความช่วยเหลือและข้อมูลในภาษา ของคุณโดยไม่เสียค่าใช้จ่าย โปรดติดต่อที่ โทร 877-475-4799.