Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC)

Effective: June 1, 2019

Next Review: November 2019
Last Review: May 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Targeted testing for specific gene variants, including EGFR and BRAF analysis, can be used to predict treatment response to targeted therapy in patients with advanced NSCLC.

MEDICAL POLICY CRITERIA

I. Testing for NTRK gene fusions and ALK, KRAS, PD-L1, and ROS1 variants may be considered medically necessary for selection of therapy.

II. Testing for EGFR gene variants (in either tumor tissue or blood) may be considered medically necessary to select patients with advanced or metastatic (stage III or IV) non-squamous cell-type non-small cell lung cancer (NSCLC) for treatment with FDA approved EGFR tyrosine kinases inhibitors as indicated. (See Policy Guidelines)

III. Tumor testing for the BRAF variants may be considered medically necessary to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with BRAF- or MEK-inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]).
IV. The Oncomine™ Dx Target test may be considered **medically necessary** to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®).

V. The following analyses/tests are considered **investigational:**

A. Testing for **EGFR** or **BRAF** variants for patients with NSCLC of squamous cell-type of any stage, or nonsquamous cell type of stage I or II

B. Testing for purposes other than treatment selection.

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

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**POLICY GUIDELINES**

The Oncomine™ Dx Target test was approved by the FDA as a companion diagnostic to aid in selecting NSCLC patients for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®). The test identifies tumors that have **EGFR** variants, **ROS1** fusions, and/or the **BRAF** V600E variant.

The FDA approved cobas® EGFR Mutation Test v2 is only intended to be used to aid in identifying patients with NSCLC whose tumors have defined **EGFR** mutations and for whom safety and efficacy of a drug have been established. This test may be run on either tumor or plasma samples.

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**LIST OF INFORMATION NEEDED FOR REVIEW**

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided, if any

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**CROSS REFERENCES**

1. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. BRAF Gene Mutation Testing To Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
4. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. In up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease.[1] Treatment of advanced NSCLC has generally been with platinum-based chemotherapy, with a median survival of 8 to 11 months and a one-year survival of 30% to 45%.[2,3] More recently, the identification of specific, targetable oncogenic “driver” variants in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Laboratory and animal experiments have shown that therapeutic interdiction of the EGFR pathway could be used to halt tumor growth in solid tumors that express EGFR.[4] These observations led to the development of two main classes of anti-EGFR agents for use in various types of cancer: small molecule TKIs and monoclonal antibodies (MAbs) that block EGFR-ligand interaction.[5] The prevalence of EGFR variants in NSCLC varies by population, with the highest prevalence in non-smoking, Asian women, with adenocarcinoma, in whom EGFR variants have been reported to be up to 30-50%. The reported prevalence in the Caucasian population is approximately 10%.[6]

Variants in two regions of 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 first and second generation tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib.[7,8] In addition, a single point mutation in exon 20 (T790M) appears to predict tumor response to third generation TKIs such as osimertinib. These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

Testing is intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the EGFR gene are considered good candidates for treatment with first and second generation TKIs. Patients with the point mutation in exon 20 (T790M), which is indicative of acquired resistance to first and second generation TKIs, are considered good candidates for third generation TKIs. Patients found to be wild-type are unlikely to respond to TKIs, so other treatment options should be considered.

BRAF

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the BRAF gene is the most frequently altered in NSCLC, in
approximately 1-3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. Most BRAF variants occur more frequently in smokers.

**KRAS**

KRAS is a G-protein involved in the EGFR-related signal transmission. The KRAS gene, which encodes RAS proteins, can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EGF receptor. Variants in the KRAS gene, mainly codons 12 and 13, have been reported in 20-30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

**REGULATORY STATUS**

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, which was released on July 14, 2011, to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

The Oncomine™ Dx Target test is an FDA approved companion diagnostic test for EGFR variants, ROS1 gene fusions, and the BRAF V600E variant, to aid in selection of the following targeted therapies:

- gefitinib (Iressa®)
- crizotinib (Xalcori®)
- dabrafenib (Tafinlar®) plus trametinib (Mekinist®).

The Oncomine™ Dx Target test is intended for patients with advanced or metastatic NSCLC.

There are two other U.S. Food and Drug Administration (FDA)-approved companion diagnostic tests for EGFR variant testing for NSCLC, intended to be used with select FDA approved EGFR tyrosine kinase inhibitors (TKIs):

- The cobas® EGFR Mutation Test v2 is a companion diagnostic test for the detection of exon 19 deletions and exon 20 and 21 (T790M and L858R, respectively) substitution variants in the EGFR gene in NSCLC tumor tissue. The FDA states:

  “The test is intended to be used as an aid in selecting patients with NSCLC for whose tumors have defined EGFR variants and for whom safety and efficacy of a drug have been established as follows:

  - Tarceva® (erlotinib) - Exon 19 deletions and L858R
  - Tagrisso® (osimertinib) - T790M”

This test (v2) was approved 11/13/2015 as a result of an expansion of the original cobas® EGFR Mutation Test to cover testing for the T790M point mutation for use of osimertinib.
• The therascreen® EGFR Rotor Gene Q polymerase chain reaction (PCR) Kit is an automated molecular assay designed to detect the presence of EGFR exon 19 deletions and the exon 21 (L858R) substitution variant in NSCLC tumor tissue. The test is intended to be used to select patients with NSCLC for whom GILOTRIF® (afatinib) or IRESSA® (gefitinib) is indicated.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The focus of the following review is on evidence related to the ability of test results to:

• Guide decisions in the clinical setting related to either treatment, management, or prevention, and
• Improve health outcomes as a result of those decisions.

The clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the EGFR gene to guide TKI treatment in patients with advanced NSCLC has been unequivocally demonstrated. Therefore, this review will focus on literature that has been published on the investigational indications described in this policy.

EGFR

Publications demonstrate that the underlying molecular mechanism underpinning dramatic responses in favorably prognostic groups of patients with advanced NSCLC appear to be the presence of activating somatic variants in the TK domain of the EGFR gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R).[7,8] These activating somatic variants are also referred to as “sensitizing” variants because there presence strongly predicts sensitivity to TKIs. Four orally administered EGFR-selective small molecules (quinazolinamine derivatives) have been approved by the FDA for use in treating NSCLC patients with sensitizing variants: erlotinib (Tarceva®, Genentech BioOncology), afatinib (Gilotrif®, Boehringer Ingelheim Pharmaceuticals, Inc), gefitinib (Iressa®, AstraZeneca), and osimertinib (Tagrisso®, AstraZeneca).

There is sufficient evidence for the clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the EGFR gene to guide TKI treatment in patients with advanced NSCLC. This evidence is published as numerous systematic reviews on monotherapies in general[12-17], clinical trials and nonrandomized studies that have been published over the past decade for the use of genetic testing to inform treatment with erlotinib[18-43], afatinib[44-49], and gefitinib[50-55].

Almost all patients who initially respond to an EGFR-TKI subsequently develop disease progression often due acquired resistance. Publications demonstrate that the underlying molecular mechanism underpinning TKI acquired resistance is the generation of the somatic point mutation in exon 20 (T790M).[56-59] This variant is also referred to as a “resistance” or
secondary variant, but can be overcome by a new class of TKIs (third generation). One orally administered EGFR-selective small molecule has been approved by the FDA for use in treating NSCLC patients with resistance variants: osimertinib (Tagrisso®, AstraZeneca).

The clinical utility of testing for the resistance variant T790M in the EGFR gene to guide treatment with third generation TKIs, such as osimertinib and rociletinib has been demonstrated in large clinical trials[60-63], and preclinical studies.[64]

**BRAF**

In June 2017, the FDA approved an additional indication for the use of dabrafenib and trametinib combination therapy in patients with NSCLC with *BRAF* V600E variant as detected by an FDA-approved test. The Oncomine™ Dx Target Test was approved as a companion diagnostic. The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled three cohorts: cohorts A and B had received at least one previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than three prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease.[65,66] Trial results for cohorts A and B have also been published.[67,68] Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy. The response rate in the 57 previously treated patients in the study that were *BRAF*-positive by local lab test was 67% (95% CI 53% to 79%) compared with 73% (95% CI 50% to 89%) for the 22 patients that were also *BRAF*-positive by Oncomine™ Dx. The response rate in the 36 treatment-naive patients that were *BRAF*-positive by local lab test was 61% (95% CI 44% to 77%) compared with 61% (95% CI 39% to 80%) in the 23 patients that were also *BRAF*-positive by Oncomine™ Dx. Additionally, a "basket" study of vemurafenib in *BRAF* V600 variant–positive nonmelanoma cancers, including 20 patients with NSCLC, was published by Hyman (2015).[69]

In summary, the response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of which had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at eight weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those that were treatment-naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. SCCs and other dermatological side effects occur.

**PRACTICE GUIDELINE SUMMARY**

**NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)**[70]

NCCN guidelines for the treatment of metastatic NSCLC (v.6.2018) recommend *EGFR, ALK, ROS1, BRAF*, and *PD-L1* testing for patients with non-squamous NSCLC (i.e., adenocarcinoma, large cell carcinoma) or NSCLC not otherwise specified. For patients with squamous cell carcinoma, the guidelines recommend *PD-L1* testing, and considering *ROS1* and *BRAF* testing. There is a further recommendation to consider *EGFR* and *ALK* testing in never smokers, small biopsy specimens, or specimens with mixed histology.

According to these recommendations, molecular testing for all advanced or metastatic NSCLC should be conducted as a part of broad molecular profiling, which should include testing for NRTK gene fusion.
Regarding KRAS, the guidelines state:

The KRAS oncogene is a prognostic biomarker. The presence of KRAS mutations is prognostic of poor survival for patients with NSCLC when compared to the absence of KRAS mutations, independent of therapy. KRAS mutations are also predictive of a lack of benefit from EFR TKI therapy. EGFR, KRAS, ROS1, and ALK genetic alterations do not usually overlap. PRRAF mutations typically do not overlap with EGFR mutations or ALK rearrangements. EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements.

COLLEGE OF AMERICAN PATHOLOGISTS, INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER, AND ASSOCIATION FOR MOLECULAR PATHOLOGY (CAP/IASLC/AMP)[71,72]

The 2014 guidelines issued jointly by the CAP/IASLC/AMP recommend:

- **EGFR** variant and **ALK** rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history);
- In the setting of fully excised lung cancer specimens, **EGFR** and **ALK** testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and
- In the setting of more limited lung cancer specimens (e.g., biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, **EGFR** and **ALK** testing may be performed in cases showing squamous cell histology. Clinical criteria (e.g., young age, lack of smoking history) may be useful to select a subset of these samples for testing.

The 2014 guidelines issued jointly by the CAP/IASLC/AMP do not recommend testing for **KRAS** variants “as a sole determinant of EGFR-targeted therapy; however, testing for KRAS may be performed initially to exclude KRAS-mutated tumors from EGFR and ALK testing as part of a stepwise algorithm designed to maximize testing efficiency.” In 2013 the CAP/IASLC/AMP panel also stated that, “The significance of **KRAS** mutational analysis may become increasingly important with the further development of new therapies targeting downstream RAS pathways, such as PI3K/AKT/mTOR and RAS/RAF/MEK, but at this time, the absence of a **KRAS** mutation does not add clinically useful information to the **EGFR** mutation result and should not be used as a determinant of EGFR TKI therapy.”[72]

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)[73]**

In 2015, the American Society of Clinical Oncology (ASCO) endorsed the 2014 CAP/IASLC/AMP joint guidelines on molecular testing to select patients with lung cancer to determine treatment. ASCO recommendations state that testing for **EGFR** should be prioritized over other molecular markers in lung adenocarcinoma.

**SUMMARY**

**NTRK GENE FUSIONS AND ALK, KRAS, PD-L1, AND ROS1**

There is enough research to show that testing for **NTRK** gene fusions and **ALK, KRAS, PD-**
*L1*, and *ROS1* variants can help to guide treatment for patients with non-small cell lung cancer (NSCLC). In addition, many clinical guidelines based on research recommend testing for patients with this disease. Therefore, *NTRK* gene fusions and *ALK, KRAS, PD-L1*, and *ROS1* genetic variant testing may be considered medically necessary for selection of therapy.

There is not enough research to show that for *NTRK* gene fusions and *ALK, KRAS, PD-L1*, and *ROS1* variants can improve health outcomes for patients when not used for treatment selection. Therefore, this testing is considered investigational when policy criteria are not met.

**EGFR**

There is enough research to show that testing for epidermal growth factor receptor (*EGFR*) variants can help to identify patients with advanced non-squamous cell-type non-small cell lung cancer (NSCLC) who are likely to benefit from certain medications. In addition, many clinical guidelines based on research recommend testing for patients with this disease. Therefore, *EGFR* genetic variant testing may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, including patients with stage I or II NSCLC or squamous cell-type NSCLC. Therefore, *EGFR* testing is considered investigational in these patients.

**BRAF**

There is enough research to show that tumor testing for the *BRAF* V600E variant can help to identify patients with advanced non-squamous cell-type non-small cell lung cancer (NSCLC) who are likely to benefit from certain medications. In addition, clinical guidelines based on research recommend testing for this variant to guide treatment for select individuals with advanced NSCLC. Therefore, tumor testing for *BRAF* variants may be considered medically necessary to select NSCLC patients for treatment with BRAF- or MEK-inhibitor therapy.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, including patients with stage I or II NSCLC or squamous cell-type NSCLC. Therefore, *BRAF* testing is considered investigational in these patients.

**ONCOMINE™ DX TARGET TEST**

The Oncomine™ Dx Target Test is an FDA-approved companion diagnostic test to help identify non-small cell lung cancer (NSCLC) patients that may benefit from certain medications. The test identifies tumors that have variants in the *EGFR, ROS1*, and *BRAF* genes, which may respond to targeted treatments. This 23-gene test also includes testing for a number of genes that do not have clear evidence of clinical utility. While genetic test panels are generally considered to be investigational when there is not clinical utility for all genes in the panel, this test is the only FDA-approved companion diagnostic available to NSCLC patients to help with selection of certain targeted medications. Therefore, use of the Oncomine™ Dx Target test may be considered medically necessary to select patients with advanced or metastatic NSCLC for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®).
There is not enough research to show that the use of the Oncomine™ Dx Target Test is useful for selecting therapy for patients without advanced or metastatic non-small cell lung cancer (NSCLC). Therefore, the use of this test is considered investigational for patients that do not meet policy criteria.

REFERENCES

14. Kato, T, De Marinis, F, Spicer, J, et al. The impact of first-line tyrosine kinase inhibitors (TKIs) on overall survival in patients with advanced non-small cell lung cancer (NSCLC) and activating epidermal growth factor receptor (EGFR) mutations: meta-analysis of


### BlueCross BlueShield Association Medical Policy Reference Manual "Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC)." Policy No. 2.04.45

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*Date of Origin: August 2010*