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**Medical Policy Manual** Genetic Testing, Policy No. 56

# *Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC)*

**Effective**: January 1, 2019

**Next Review:** November 2019
**Last Review:** November 2018

## 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

*EGFR* and *BRAF* analysis can be used to predict treatment response to targeted therapy in patients with advanced NSCLC.

## MEDICAL POLICY CRITERIA

**Note:** This policy does not address genetic analyses/tests for the *ALK*, *PD-L1* or *ROS1* genes, which may be considered medically necessary.

I. 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)

II. 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®]).

III. 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®).

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

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

B. Testing for *EGFR* or *BRAF* variants for purposes other than treatment selection.

C. Testing for variants of the *KRAS* gene as a technique to predict treatment nonresponse to EGFR tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC

D. Testing for variants in other genes including, but not limited to *RET*, *MET*, and *HER2*, for targeted therapy in patients with NSCLC

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

## POLICY GUIDELINES

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
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided, if any

The Oncomine™ Dx Target test was approved by the FDA as a companion diagnostic to aid is 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.

Please see the Regulatory Status section, above, for a list of FDA indications for use. For further information on the approved indications for these tests please visit the FDA website for approved companion diagnostic devices.

## 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. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46
6. Molecular Testing in the Management of Pulmonary Nodules, Laboratory, Policy No. 73
7. Medication Policy Manual, Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

## BACKGROUND

### 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.[9] 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 EFG 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.

### *RET*

*RET* (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported.[9] *RET* fusions occur in 0.6-2% of NSCLCs and in 1.2-2% of adenocarcinomas.

### *MET*

MET amplification is one of the critical events for acquired resistance in *EGFR*-variant adenocarcinomas refractory to EGFR-TKIs.[9]

### *HER2*

Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of TK receptors, and has no specific ligand.[9] When activated, it forms dimers with other EGFR family members. HER2 is expressed in approximately 25% of NSCLC. *HER2* variants are detected mainly in exon 20 in 1-2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

## 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,[8] 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 to 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.

### *KRAS*

### KRAS and EGFR Tyrosine Kinase Inhibitors (TKIs)

Systematic Reviews

Pan (2016) published a meta-analysis of 41 studies (total n=13,103 patients) of prognostic and predictive values of the *KRAS* variant in NSCLC.[70] *KRAS* variant was significantly associated with poorer overall survival (OS) (hazard ratio [HR] 1.6, 95% CI 1.4 to 1.8) and DFS (HR 1.57, 95% CI 1.2 to 2.1) in early-stage resected NSCLC, and with inferior outcomes of EGFR-TKIs treatment (relative risk [RR] 0.21, 95% CI 0.1 to 0.4) in advanced NSCLC. A *KRAS* variant was still significantly associated with poorer OS (HR 1.4, 95% CI 1.2 to 1.6) and PFS (HR 1.4, 95% CI 1.1 to 1.6) of EGFR TKIs when patients with *EGFR* variants were excluded. The reviewers concluded that *KRAS* variants are weak, but valid predictors of poor prognosis and TKI treatment outcomes in NSCLC. Limitations of this review include the inclusion of unpublished (incomplete) clinical trials and lack of complete genetic information in a number of included studies.

Ying (2015) conducted a meta-analysis including twelve prospective intervention trials comprised of 1,859 unselected advanced NSCLC patients.[71] The presence of a *KRAS* variant was associated with shorter OS and PFS (HR 2.09, 95% CI 1.56 to 2.80; HR 1.82, 95% CI 1.50 to 2.20, respectively) in patients. Four retrospective studies on the role of *KRAS* status in *EGFR* wild-type advanced NSCLC were included in the analysis and concluded that the presence of a *KRAS* variant was not associated with any of the outcomes in *EGFR* wild-type patients treated with EGFR-TKIs. The authors concluded that *KRAS* variants could be used as a potential negative predictor of clinical benefit from EGFR-TKIs, but that *KRAS* testing is of limited value to identify patients for EGFR-TKIs when *EGFR* status is considered.

Qi (2013) performed a meta-analysis that included eight randomized controlled trials (n=2,417) with significant methodological limitations. The authors reported this the results of this analysis demonstrated a survival benefit of combining targeted therapy for advanced NSCLC; however, progression-free survival for patients with *EGFR*-variant or wild-type *KRAS* favored monotherapy erlotinib.[72] Sub-group analysis based on phases of trials showed a tendency to improve PFS and OS in combining targeted therapy. Moreover, it should be noted that not all of the trials analyzed, including two phase 3 trials, demonstrated OS benefits from combining therapies. There were several limitations in this meta-analysis, such as the lack of individual patient data - an individual patient data-based meta-analysis produces a more reliable estimation than one based on abstracted data. Possible survival benefits could not be determined in studies when patient clinical variables (staging, age, histologic types and

general physical conditions) were unknown. In addition, different treatment duration and different combining of targeted therapies were both potential factors that increased heterogeneity amongst trials. Phase 2 and phase 3 trials were combined in this study and thus presented an additional study limitation. Finally, publication bias was possible because papers with null results tend not to be published.

Mao (2010) evaluated the association between *KRAS* variants and resistance to TKIs with NSCLC, using a meta-analysis of 22 studies that included 1,470 NSCLC patients, of whom 16% had *KRAS* variants (n=231).[73] This study suggests that *KRAS* variants may represent negative predictive biomarkers for tumor response in NSCLC patients treated with EGFR-TKIs. However, due to a mutually exclusive relationship between *KRAS* and *EGFR* variant and no difference in survival between *KRAS* mutant/*EGFR* wild-type and *KRAS* wild-type/*EGFR* wild-type NSCLC, the clinical usefulness of a *KRAS* variant as a selection marker for EGFR-TKIs sensitivity in NSCLC is limited.

A meta-analysis by Linardou (2008) assessed whether *KRAS* variants represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in NSCLC.[74] Authors stated “substantial” evidence was found in the literature that determined *KRAS* variants were appropriate markers for the identification of a subgroup of patients (20% of patients with NSCLC) with a limited probability of responding to EGFR-targeted treatments. In the meta-analysis, the presence of a *KRAS* variant was significantly associated with an absence of response to TKIs; however, the pooled sensitivity was low (0.21, 95% CI 0.16 to 0.28). In summary, the findings of this study suggested that somatic variants leading to gain-of-function and constitutive signaling of the *KRAS* pathway(s) represent a strong candidate predictive biomarker for non-responsiveness to TKI-based strategies. Authors advocated for a large cooperative prospective study that would address the prognostic and predictive value of *KRAS* in predicting the efficacy of EGFR-targeted agents in lung cancer due to the limitations of this study. These limitations included the unavailability of individual patient data, inadequate reporting of survival data, heterogeneity of response endpoints, intrinsic differences in the treatment regimens, patient selection criteria, and retrospective analysis of studies.

Randomized Controlled Trials

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from a small number of phase 2 and phase 3 trials and retrospective single-arm studies.[31-36,75-77] The majority of identified studies had significant methodological limitations including small sample size, variance in study populations (older individuals ≥70 and females), and inconsistent staging information. Representative studies are described below:

Papadimitrakopoulou (2016) reported results of the BATTLE-2 phase 2 study in 2016.[78] The BATTLE-2 study evaluated effects of targeted therapies focusing on *KRAS*-mutated cancers. Two hundred patients with advanced NSCLC tumors who did not have *EGFR* variants or *ALK* gene fusions, whose cancer was refractory to more than one prior therapy, were assigned to one of four arms using adaptive randomization: erlotinib (n=22), erlotinib plus MEK inhibitor, MK-2206 (n=42), MK-2206 plus and AKT inhibitor AZD6244 (n=75), or sorafenib, a multi-target TKI (n=61), stratified by *KRAS* status. Only 186 evaluable patients were included in analyses. The eight-week disease control rate was 20%, 25%, 62%, and 44% for the four treatment groups, respectively, in the *KRAS* variant-positive patients. For *KRAS* wild-type patients, disease control rate was 36%, 57%, 49%, and 47%, respectively. Median PFS did not differ by *KRAS* status.

Rulli (2015) reported results from biomarker analyses in the TAILOR trial.[79] TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for *KRAS* and *EGFR* variant status. Wild-type *EGFR* patients (n=218) received first-line platinum-based chemotherapy and then were randomly allocated at progression to erlotinib or docetaxel. *KRAS* variants were present in 23% of randomized patients. The presence of a *KRAS* variant was not associated with PFS (HR 1.01, 95% CI 0.71 to 1.41, p=0.98) or OS (HR 1.24, 95% CI 0.87 to 1.77, p=0.23). The treatment effect did not differ by *KRAS* status (test for interaction: OS p=0.97, PFS p=0.42). The authors concluded that in this trial, *KRAS* was neither prognostic nor predictive of benefit for either docetaxel or erlotinib.

Fiala (2013) reported on a retrospective analysis of patients with squamous cell NSCLC who underwent *EGFR*, *KRAS*, and *PIK3CA* (phosphatidylinositide-3-kinase catalytic subunit-alpha) variant testing.[80] Of 215 patients tested, 16 (7.4%) had a variant *KRAS*. Of 174 tested patients who were treated with an EGFR-TKI (erlotinib or gefitinib), median PFS in 14 *KRAS*-variant patients was 1.3 months versus 2.0 months in *KRAS* wild-type patients (n=160 [92%]); the difference was not statistically significant (Kaplan-Meier [KM] log-rank test p=0.120). Median OS in this treated group was 5.7 months in *KRAS*-variant patients versus 8.2 months in *KRAS* wild-type patients, a statistically significant difference (KM log-rank test p=0.039). The authors concluded that there was no role identified for *EGFR, KRAS, PIK3CA* variants in the prediction of EGFR-TKIs efficacy in patients with advanced-stage squamous cell NSCLC.

Guan (2013) reported on 1,935 consecutive patients with NSCLC who were treated at a single institution.[81] Patients with mutated *KRAS* were randomly matched on tumor, node, metastasis (TNM) stage, time of first visit within one year, and histology, to both *EGFR* variant-positive and *KRAS/EGFR* wild-type patients. Seventy patients (4%) received EGFR-TKI therapy. In this group, median PFS was 11.8 and 2.0 months in patients with *EGFR* and *KRAS* variants, respectively, and 1.9 months in wild-type patients; in comparison to wild-type patients, PFS was statistically longer in patients with *EGFR* variants (p<0.001) but not different in patients with *KRAS* variants (p=0.48). The authors observed that “the presence of an *EGFR* variant, but not a *KRAS* variant, was predictive of responsiveness to *EGFR* TKI treatment.”

Pao (2015) provided analysis on 60 drug-sensitive adenocarcinomas; 9 out of 38 (24%) had *KRAS* variants, while none of the drug-sensitive tumors had variants.[75] These data indicate that tumors with the *KRAS* variant are associated with a lack of response to these kinase inhibitors, suggesting that patients whose lung adenocarcinomas have *KRAS* variants will not experience significant tumor regression with either gefitinib or erlotinib. Whether *KRAS* variant status can be used to predict responses to erlotinib in patients is still under investigation. Data presented here suggested that clinical decisions regarding the use of these agents in patients with lung adenocarcinomas might be improved in the future by pre-treatment variant profiling of *KRAS*. These findings warrant validation in large prospective trials using standardized variant detection techniques.

Eberhard (2005) detected *KRAS* variants in 21% of tumors from their patient population and determined an association of the variant with significantly decreased time to progression and survival in erlotinib plus chemotherapy-treated patients.[33] However, authors stated that further studies are needed to confirm the findings of their retrospective subset analysis.

In an additional study, the effect of *KRAS* variant on the response to erlotinib treatment was analyzed in 206 tumors; 15% of patients had *KRAS* variants.[36] Erlotinib response rates were 10% for wild-type and 5% for mutant *KRAS*. Significant survival benefit from erlotinib therapy

was observed for patients with wild-type *KRAS* but not for patients with mutant *KRAS*. In multivariate analysis, *KRAS* was not a prognostic for poorer survival or predictive of differential survival benefit from erlotinib.

Schneider (2008) sequenced tumor samples from patients with stage IIIB/IV NSCLC.[32] None of 17 patients with a *KRAS* variant had a tumor response. Authors suggest prospective, placebo-controlled studies are needed to determine the predictive value of the putative biomarkers.

In a 2012 study of 246 NSCLC patients, the presence of *KRAS* variants in plasma was suggested to be a marker of poor prognosis and thought to hold predictive value.[82] Patients with a detectable plasma- *KRAS* variant had a significantly shorter overall survival and progression-free survival compared to patients without the *KRAS* variant. The response rate to chemotherapy was significantly lower in the group of patients with a variant compared to patients without the variant. Further validation of an independent cohort is needed.

Section Summary

It remains unclear whether assessment of *KRAS* variant status will be clinically useful regarding anti-EGFR therapy in the treatment of NSCLC. Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from a number of studies, including retrospective single-arm studies, prospective studies, phase 2 trials and phase 3 trials that conducted non-concurrent subgroup analyses of the efficacy of TKIs in patients with wild-type versus variant *KRAS* lung tumors. Although studies have shown that a *KRAS* variant in patients with NSCLC confers a high level of resistance to TKIs, data are insufficient to make a determination about an association between *KRAS* variant status and survival in these patients.

### *KRAS* and Anti-EGFR Monoclonal Antibodies

Two phase 3 trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC.[83,84] Subsequently, an investigation of *KRAS* variant status and cetuximab treatment was performed from both trials.[85,86] Outcomes observed (overall survival and/or progression free survival) in the cetuximab-containing and chemotherapy alone arms were similar between patients with mutant and wild-type *KRAS*. However, these findings should be interpreted with caution given the small subgroup sample size and retrospective nature of the analysis.

Section Summary

While a lack of response to the *EGFR* monoclonal antibodies has been established in metastatic colorectal cancer and use of these drugs is largely restricted to patients with wild-type *KRAS*, the expectation that *KRAS* variant status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In two randomized trials with non-concurrent subgroup analyses of *KRAS* variant status and the use of cetuximab with chemotherapy, *KRAS* variants did not appear to identify patients who would not benefit from anti-*EGFR* antibodies, as the outcomes observed with cetuximab were regardless of *KRAS* variant status.

## OTHER ONCOGENIC VARIANTS

Other potentially targetable oncogenic variants have been characterized in lung adenocarcinomas including in the genes *RET*, *MET*, and *HER2*. The data on the use of targeted therapies in NSCLC with a variant in one of these genes is preliminary in that much of the demonstrated sensitivity of tumor to the various drugs has been in vitro or in animal studies, and published data on patient tumor response and survival outcomes are extremely limited, consisting of case reports and small case series.

The following studies are representative of the available published evidence for these investigational genes.

### *RET*

In a phase 2 prospective trial for patients with *RET* fusion-positive tumors, preliminary data on three patients treated with cabozantinib showed a partial response in two patients, and one with stable disease approaching eight months.[87]

Yoh (2017) presented results of an open-label phase 2 trial (LURET) in which patients with NSCLC with RET rearrangements who had received at least one previous chemotherapy treatment, were administered vandetanib therapy.[88] Nine of the 17 patients achieved an objective response.

### *MET*

Ye (2016) conducted a meta-analysis to determine the efficacy and risk profile of c-met inhibitors in NSCLC, including nine studies (n=1,611 patients in target drug groups and 1,605 patients in control groups).[89] Patients in target drugs group had longer PFS (HR 0.80, 95% CI 0.66 to 0.99, p=0.04) but not OS than those in control group, especially in Asian (HR 0.57, 95% CI 0.42 to 0.76, p<0.001), Non-squamous (HR 0.79, 95% CI 0.64 to 0.97, p=0.03), phase 3 (HR 0.66, 95% CI 0.50 to 0.86, p=0.002), previous treated (HR 0.77, 95% CI 0.63 to 0.95, p=0.01) and small molecular compounds subgroups (HR 0.62, 95% CI 0.50 to 0.78, p<0.001). In addition, target drugs did not affect the objective response rate (ORR) but improved disease control rate (RR 1.22, 95% CI 1.02 to 1.46, p=0.03) of NSCLC patients.

Dimou (2014) performed a meta-analysis to assess the effect of high *MET* gene copy number on the overall survival of patients with advanced NSCLC.[90] Nine retrospective studies were included that reported data regarding the prognostic impact of *MET* gene copy number on the survival of patients with NSCLC who had received surgery. All of the included studies had populations of patients with mixed adenocarcinoma histology results. The authors reported that *MET* gene copy number predicted poorer overall survival when all studies were combined in a random effects model (HR 1.78, 95% CI 1.22 to 2.60). When only the studies that had at least 50% of adenocarcinoma patients in their populations were included, the effect was significant (five studies, HR 1.55, 95% CI 1.23 to 1.94). This was not true when we included only the studies with no more than 50% of the patients having adenocarcinoma histology (four studies HR 2.18, 95% CI 0.97 to 4.90). The authors concluded that higher *MET* gene copy number in the primary tumor at the time of diagnosis predicts worse outcome in patients with NSCLC, however, this may be specific to the subset of the patients with adenocarcinoma histology.

A phase 2 trial of *MET*-positive NSCLC, in which patients were treated with an anti-MET antibody plus erlotinib, showed improved PFS and OS.[91]

### *HER2*

Mok (2016) reported on the biomarker subgroup analyses from the FASTACT-2 study in 2016.[92] FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study of intercalated first-line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIB or IV NSCLC. In addition to analyzing for *EGFR* variants, HER2 and HER3 biomarkers were analyzed by immunohistochemistry. Only *EGFR* variants (p<0.001) were predictive of outcomes; HER2 and HER3 biomarkers were not significant in a treatment-by-biomarker interaction test.

Shen (2015) retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for HER2 expression.[93] HER2 overexpression was detected in 24 patients. The ORR in patients with and without HER2 overexpression was 29% and 14%, respectively (p=0.12). Median PFS and OS in patients with and without HER2 overexpression did not differ statistically significantly (PFS, 4.7 months vs 3.9 months, p=0.09; OS, 21 months vs 19 months, p=0.09).

Mazières (2013) reported on a retrospective review of a consecutive series of patients with NSCLC who were tested for a *HER2* variant, and the authors assessed clinicopathologic characteristics and patient outcomes according to variant status.[94] A *HER2* variant was identified in 65 of 3800 (1.7%) patients, and was mutually exclusive of other driver variants (*EGFR*, *ALK*, *BRAF*), with the exception of one case in which both a *HER2* and *KRAS* variant were identified. The patient population in which a *HER2* variant was found had a median age of 60 years (range 31 to 86), 69% were women, and 52% were never-smokers. All of the tumors were adenocarcinomas, and 50% were stage IV (n=33). The patients with stage IV disease received conventional chemotherapy, and of these, 16 patients also received HER2-targeted therapy as additional lines of therapy (for a total of 22 individual anti-HER2 treatments that were evaluable). Four patients had progressive disease, seven had disease stabilization, and 11 had a partial response. PFS for patients with HER2 therapies was 5.1 months.

Section Summary

The data on the use of targeted therapies in NSCLC with a variant in *RET*, *MET*, or *HER2* is preliminary and limited to a few case reports, retrospective analyses, and case series. Further studies are needed to determine whether testing for genetic alternation in these genes may be useful for targeted therapy in patients with NSCLC.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)[95]

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.

### COLLEGE OF AMERICAN PATHOLOGISTS, INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER, AND ASSOCIATION FOR MOLECULAR PATHOLOGY (CAP/IASLC/AMP)[96,97]

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."[97]

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)**[98]

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

***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.

**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®).

***KRAS***

*KRAS* variants may be an indicator of poor prognosis in non-small cell lung cancer (NSCLC) and may predict a lack of response to tyrosine kinase inhibitors (TKIs). However, there is not enough research to show that KRAS testing can help with treatment selection and improve health outcomes for patients with NSCLC. Therefore, analysis of variants of the *KRAS* gene is considered investigational for predicting treatment non-response in NSCLC.

**OTHER ONCOGENIC VARIANTS**

*RET*, *MET*, and *HER2* variants have been studies as potential targets for non-small cell lung cancer (NSCLC) treatment. However, there is not enough research to show that testing for these variants can improve health outcomes for non-small cell lung cancer (NSCLC) patients. Therefore, testing *RET*, *MET*, and *HER2* genes for targeted therapy in patients with NSCLC is considered investigational.

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## CODES

| Codes | Number | Description |
|---|---|---|
| CPT | 0022U | Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider |
| | 81210 | *BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)* |
| | 81235 | EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) |
| | 81275 | KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in exon 2 (eg, codons 12 and 13) |
| | 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) |
| | 81404 | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) – which includes *RET* (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F) |
| | 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) – which includes *KRAS* (Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence; and *RET* (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16) |

| Codes | Number | Description |
|---|---|---|
| | 81406 | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – which includes *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence |
| | 81479 | Unlisted molecular pathology procedure |
| | 84999 | Unlisted chemistry procedure |
| | 88363 | Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis) |
| HCPCS | None | |

***Date of Origin:*** *August 2010*