Protocol

Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Medical Benefit		**Effective Date**: 06/01/20	**Next Review Date**: 03/21
Preauthorization	No	**Review Dates**: 05/09, 05/10, 05/11, 05/12, 05/13, 05/14, 01/15, 01/16, 07/16, 07/17, 09/17, 01/18, 09/18, 03/19, 03/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for EGFR variants or ALK rearrangements	Comparators of interest are: • Management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for BRAF variants or ROS1 rearrangements	Comparators of interest are: • Management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for KRAS or HER2 variants, RET rearrangements or MET amplifications	Comparators of interest are: • Management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

DESCRIPTION

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes that may direct targeted therapy depending on the presence of specific variants.

SUMMARY OF EVIDENCE

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for epidermal growth factor receptor (EGFR) variants and ALK rearrangements, the evidence includes

phase 3 studies comparing tyrosine kinase inhibitors (TKIs; e.g., afatinib, erlotinib, gefitinib, osimertinib) with chemotherapy. The relevant outcomes are overall survival (OS), disease-specific survival, test validity, quality of life (QOL), and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival (PFS), with a reduction in toxicity and improvement in the QOL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for BRAF variants and ROS1 rearrangements, the evidence includes nonrandomized trials and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. The relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that combination therapy with dabrafenib and trametinib for BRAF V600E-variant NSCLC and crizotinib for NSCLC with ROS1 rearrangements result in response rates of 60% and 70%, respectively, with acceptable toxicity profiles. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for KRAS or HER2 variants, RET rearrangements, or MET amplification, the evidence includes for KRAS post hoc analyses trials, observational studies, and meta-analyses; for the other variants, the evidence includes a phase two trial with preliminary data and retrospective analyses of very small case series and case reports. The relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that KRAS variants in patients with NSCLC confer a high level of resistance to TKIs; data are insufficient to assess any additional benefit to testing for KRAS variants to select for EGFR TKIs beyond EGFR testing. In two randomized trials with post hoc analyses of KRAS variant status and use of the anti-EGFR monoclonal antibody cetuximab with chemotherapy, KRAS variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of KRAS variant status. In two randomized controlled trials of advanced KRAS-variant positive disease, MEK inhibitors did not improve PFS compared with docetaxel. Studies for HER2, RET, and MET variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive NTRK gene fusion testing, the evidence includes prospective observational studies. The relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In 55 patients with consecutively and prospectively identified tropomyosin receptor kinase fusion-positive solid tumors, including four patients with lung tumors, the overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive tumor mutational burden testing, the evidence includes a randomized controlled trial and retrospective observational studies. In a subgroup analysis of an ongoing randomized controlled trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden (>10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher tumor mutational burden and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Gene variant analysis to classify non-squamous, NSCLC may be considered **medically necessary** for genes that identify targets for molecular therapy or guide therapy under the following circumstances (see Policy Guidelines for appropriate targeted therapy):

- At initial diagnosis: EGFR, ALK ROS1, MET, BRAF, and KRAS variants;
- In advanced or metastatic disease: EGFR, ALK, ROS1, MET, BRAF, and KRAS variants.

EGFR T790M testing may be considered **medically necessary** for individuals with first order family members who have Hereditary Lung Cancer Syndrome with EGFR T790M germline variants.

Analysis for other EGFR variants within exons 18-24, or other applications related to NSCLC, is **medically necessary**.

PD-L1 testing may be considered **medically necessary** in advanced or recurrent disease when therapy with nivolumab or pembrolizumab is being considered.

Analysis of the BRAF V600E variant may be considered **medically necessary** to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis for genetic alterations in the BRAF gene for targeted therapy in patients with NSCLC in all other situations is considered **investigational**.

Analysis of two types of somatic variants within the EGFR gene – small deletions in exon 19 and a point mutation in exon 21 (L858R) - is considered **investigational** for patients with advanced non-small-cell lung cancer (NSCLC) of squamous cell-type.

Analysis of somatic rearrangement variants of the ALK gene is considered **investigational** in all other situations.

BAP1 gene testing to identify high risk for developing mesothelioma is considered **investigational**.

Genetic testing using multi-gene panels and NGS that tests for more than those genes considered medically necessary in the above policy statements (EGFR, ALK, ROS1, MET, KRAS, BRAF, PD-L1) is considered **investigational**.

POLICY GUIDELINES

EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], or afatinib [Gilotrif®]), may be indicated in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Analysis for the T790M variant in the gene for the EGFR may be indicated to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy.

ALK inhibitor therapy (e.g., crizotinib [Xalkori®] or ceritinib [Zykadia™]) may be indicated in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

These gene tests are intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutations in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are considered good candidates for treatment with erlotinib, gefitinib or afatinib. Patients with wild type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered.

The 2018 guidelines from the National Comprehensive Cancer Network recommend that EGFR variants and ALK rearrangement testing (category 1) as well as ROS1 and BRAF testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:

"One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: EGFR, ALK, and ROS1. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: BRAF, MET, RET, ERBB2 (HER2), and KRAS, if adequate material is available. KRAS testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication."

MEDICARE ADVANTAGE

For Medicare Advantage, the following gene analysis is considered **medically necessary** in patients who have non-small-cell lung cancer when needed to determine if a Medicare covered therapy is a reasonable option given the individual's specific clinical presentation:

- BRAF gene analysis
- KRAS gene analysis, variants in codons 12 and 13
- KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis additional variant(s) (e.g., codon 61, codon 146)
- MET proto-oncogene, receptor tyrosine kinase
- ROS proto-oncogene 1, receptor tyrosine kinase

EGFR testing, common variants, (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) [when specified as EGFR mutation analysis testing] is considered **medically necessary** as a technique to predict treatment response for individuals with non-small-cell-lung cancer undergoing treatment with EGFR tyrosine kinase inhibitor (TKI) therapy (for example, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]).

For Medicare Advantage Genomic Sequential Analysis Panel will be considered **medically necessary** in the evaluation of tumor tissue in the following clinical circumstances:

- Newly diagnosed patients with advanced (stage IIIB or IV) NSCLC, who are not treatable by resection or radiation with curative intent, and who are suitable candidates for therapy at the time of testing.
- Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have not responded to at least one systemic therapy, or who have progressed following resection. The patient must be a candidate for treatment at the time of the testing.
- Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have been resistant to at least one targeted therapy, are able to undergo tumor tissue biopsy for testing, and who are suitable candidates for additional treatment at the time of testing.

Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, five to 50 genes may be used as long as the panel contains, at a minimum, five or more gene tests for molecular biomarkers determined to meet Medicare Advantage criteria as listed above.

For Medicare Advantage Next Generation Sequencing (NGS) as a diagnostic laboratory test is **medically necessary** when performed in a Clinical Laboratory Improvement Amendments CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
    a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
    b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
    c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
2. The diagnostic laboratory test using NGS must have results provided to the treating physician for management of the patient using a report template to specify treatment options.

BACKGROUND

NON-SMALL-CELL LUNG CANCER

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease.[1] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of eight to 11 months and one-year survival of 30% to 45%.[2,3] The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. Testing for epidermal growth factor receptor (EGFR) variants and anaplastic lymphoma kinase (ALK) rearrangements is routine in clinical decision making for the treatment of NSCLC. The use of testing for other variants to direct targeted therapy continues to evolve.

EGFR Gene

EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule tyrosine kinase inhibitors [TKIs]). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors, such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Variants in two regions of the EGFR gene (exons 18-24)-small deletions in exon 19 and a point variant in exon 21 (L858R)-appear to predict tumor response to TKIs such as erlotinib. Likewise, tumors with an acquired exon 20 (T790M) substitution variant appear to respond to osimertinib following the failure of TKI therapy.

The prevalence of EGFR variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma, in whom EGFR variants have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

ALK Gene

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK 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.

The EML4-ALK rearrangement ("ALK-positive") is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

BRAF Gene

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 mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants.[4] Most BRAF variants occur more frequently in smokers.

ROS1 Gene

ROS1 codes for a receptor TK of the insulin receptor family and chromosomal rearrangements result in fusion genes. The prevalence of ROS1 fusions in NSCLC varies from 0.9% to 3.7%.[4] Patients with ROS1 fusions are typically never-smokers with adenocarcinoma.

KRAS Gene

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

EGFR, ALK, ROS1, and KRAS driver mutations are considered to be mutually exclusive.

HER2 Gene

Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. 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% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.[4]

RET Gene

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.[4] RET fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.[4]

MET Gene

MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR TKIs.[4]

NTRK Gene Fusions

NTRK gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK gene fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers.[5]

Tumor Mutational Burden

Tumor mutational burden is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.[6]

Targeted Therapies

Four orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa; AstraZeneca), erlotinib (Tarceva; OSI Pharmaceuticals), afatinib (Gilotrif; Boehringer Ingelheim), and osimertinib (Tagrisso; AstraZeneca). Gefitinib, erlotinib, afatinib, and osimertinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC when EGFR status is confirmed through a companion diagnostic test.

Crizotinib is an oral small-molecule TKI that is FDA-approved for patients with locally advanced or metastatic NSCLC who are positive for the ALK or ROS1 gene rearrangements confirmed through a companion diagnostic test. Ceritinib is a potent ALK inhibitor that is approved for ALK-positive patients whose cancer has progressed while taking crizotinib or who could not tolerate crizotinib. Alectinib is a selective ALK inhibitor with high central nervous system penetration that is active against several secondary resistance variants to crizotinib. Brigatinib is also an ALK inhibitor that may be able to overcome a broad range of the resistance mechanisms in patients who have progressed on or are intolerant to crizotinib.

BRAF or MEK inhibition with TKIs (e.g., vemurafenib/dabrafenib or trametinib) was originally approved by the FDA for treatment of unresectable or metastatic melanoma with BRAF V600 variants confirmed through a companion diagnostic test. The combination of dabrafenib and trametinib was approved for the treatment of metastatic NSCLC in 2017 for patients with confirmed BRAF V600 variants.

For the treatment of KRAS-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not used in NSCLC.

Larotrectinib was approved in 2018 for the treatment of patients with solid tumors harboring an NTRK gene fusion. There is currently no FDA approved companion diagnostic test for larotrectinib. The clinical review states, "The clinical review team and CDRH agreed that it is in the best interest of U.S. patients to approve larotrectinib before one or more companion diagnostic assays are ready for a PMA submission. Loxo Oncology has agreed to a postmarketing commitment to work with diagnostic developers to develop an analytically and clinically validated companion diagnostic test for the selection of patients with NTRK fusion-positive solid tumors for whom larotrectinib is safe and effective."[7]

Nivolumab in combination with iplimumab has been investigated as a treatment option for patients with NSCLC with tumor mutational burden more than ten mutations per megabase. There is no FDA companion diagnostic test for tumor mutational burden.

Targeted therapies currently under investigation and not FDA-approved for the remaining genetic alterations in NSCLC are trastuzumab and afatinib for HER2variants, crizotinib for MET amplification, and cabozantinib for RET rearrangements.

REGULATORY STATUS

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.[7-17]

Table 1. FDA-Approved Targeted Treatment for NSCLC and Companion Diagnostic Tests

Treatment	Indication	FDA Approval of Companion Diagnostic Test
Afatinib (Gilotrif)	• 2013: First line for patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R)	• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction

Treatment	Indication	FDA Approval of Companion Diagnostic Test
	substitutions • 2016: Second line for patients with metastatic squamous NSCLC • 2018: First line for patients with nonresistant EGFR variants other than exon 19 or exon 21 NSCLC	(RGQ PCR) kit (Qiagen) • 2017: FoundationOne CDx™ (Foundation Medicine)
Alectinib (Alecensa)	• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive NSCLC who have not received prior systemic therapy for metastatic disease	• 2017: FoundationOne CDx™ (Foundation Medicine)
Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib	• Test not specified in FDA approval
Ceritinib (Zykadia)	• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive metastatic NSCLC	• 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine)
Crizotinib (Xalkori)	• 2011: First line for patients with ALK-positive metastatic NSCLC	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine)
Crizotinib (Xalkori)	• 2016: Patients with ROS1-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Dacomitinib (Vizimpro)	• 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions	• Test not specified in FDA approval
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)
Erlotinib (Tarceva)	• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy • 2004: Second line for patients with locally advanced or metastatic NSCLC	• 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics) • 2017: FoundationOne CDx™ (Foundation Medicine)
Gefitinib (Iressa)	• 2015: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions 2003: Second line for patients with locally advanced or metastatic NSCLC	• 2015: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit • 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics)
Osimertinib (Tagrisso)	• 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by FDA-approved test, who have not responded to EGFR-blocking therapy	• 2015: cobas® EGFR Mutation Test v2 (blood test) • 2017: FoundationOne CDx™

Treatment	Indication	FDA Approval of Companion Diagnostic Test
	• 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants	(Foundation Medicine)
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that o have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, o are metastatic or where surgical resection is likely to result in severe morbidity, and o have no satisfactory alternative treatments or that have progressed following treatment.	• Test not specified in FDA approval

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; FDA: Food and Drug Administration; FISH: fluorescence in situ hybridization; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

RELATED PROTOCOLS

Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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135. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date For services performed on or after 10/03/2019.
136. National Coverage Determination (NCD) for NEXT GENERATION SEQUENCING (NGS) (90.2), Implementation Date 4/8/2019.