Corporate Medical Policy

Testing for Targeted Therapy of Non-Small-Cell Lung Cancer AHS - M2030

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Description of Procedure or Service

Non-small cell lung cancer (NSCLC) is a heterogeneous group of cancers encompassing any type of epithelial lung cancer other than small cell lung cancer (SCLC) which arise from the epithelial cells of the lung and include squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLCs are associated with cigarette smoke; however, adenocarcinomas may be found in patients who have never smoked (Alberg, Ford, & Samet, 2007). Recently oncogenesis in NSCLC has been associated with mutations in the epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) gene or ROS1 gene (L. Sequist & Neal, 2017).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for testing for targeted therapy of non-small-cell lung cancer when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Testing for Targeted Therapy of Non-Small-Cell Lung Cancer is covered

Testing for targeted therapy of non-small-cell lung cancer (NSCLC) is medically necessary for EGFR and BRAF mutations, ALK and ROS1 rearrangements before any systemic therapy initiation in patients with advanced stage (IIIB or IV) who meet the following criteria:

A. Individuals with adenocarcinoma, large cell or NSCLC not otherwise specified; OR
B. Individuals with squamous cell carcinoma who:
   1. Have never smoked; OR
   2. Have mixed non-squamous and squamous histology; OR
   3. When the histologic diagnosis of squamous cell carcinoma is based on a small biopsy specimen.

Reimbursement is allowed for analysis of PD-L1 expression by immunohistochemistry in NSCLC before therapy with pembrolizumab.
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Testing for NTRK gene fusion is considered medically necessary for individuals with metastatic or advanced NSCLC before first-line or subsequent therapy with larotrectinib or entrectinib.

Microsatellite instability analysis is considered medically necessary for individuals with unresectable or metastatic NSCLC that has progressed after prior treatment and for which there is no alternative treatment AND for whom pembrolizumab is being considered for therapy.

**When Testing for Targeted Therapy of Non-Small Cell Lung Cancer is not covered**

- Analysis for all other genetic alterations for targeted therapy, not mentioned above, (including but not limited to MET, RET, KRAS and ERBB2) in patients with NSCLC is considered investigational.
- Analysis of tumor mutational burden (TMB) for targeted therapy is considered investigational.

**Note:** For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

**Policy Guidelines**

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide. Non-small cell lung cancers (NSCLCs) account for 85%-90% of lung cancers, while small-cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades (Jemal et al., 2011).

An improved understanding of the molecular and immune pathways that drive malignancy in NSCLC, as well as other neoplasms, most notably mutations in the epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) gene or ROSI gene, has led to the development of specific molecular treatments for patients (L. Sequist & Neal, 2017).

PD-L1 expression testing via immunohistochemistry is used to guide therapy for patients with non-small cell lung cancer. This testing shows that specific antigens are present in tumor tissue. Tumor cells present PD-L1 (programmed death-1 ligand) to T-cells to inhibit the immune response by downregulating cytokine production and T-cell proliferation. Monoclonal antibody therapy (immune therapy) has been developed to inhibit this pathway and allow for the body’s own immune system, in patients with higher levels of PD-L1 expression, to fight the cancer more effectively.

Microsatellite instability testing has also been used with guide therapy in with solid tumors such as non-small cell lung cancer. Microsatellite instability is the occurrence of microsatellite markers (highly polymorphic mono- and dinucleotide microsatellite repeats) in tumor cells and is associated with dysfunctional DNA mismatch repair. In cells with high microsatellite instability, the resulting DNA replication gene sequences are not preserved as they should be. Testing is done via multiplex polymerase chain reaction amplification.

EGFR - Mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase are observed in approximately 15 percent of NSCLC adenocarcinoma in the United States and occur more frequently in nonsmokers(Kawaguchi et al., 2016). In advanced NSCLC, the presence of an EGFR mutation confers a more favorable prognosis and strongly predicts for sensitivity to EGFR tyrosine kinase inhibitors. (TKIs) such as erlotinib, gefitinib, afatinib, and osimertinib (L. Sequist & Neal, 2017).
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ALK - Translocations involving the anaplastic lymphoma kinase (ALK) tyrosine kinase are present in approximately 4 percent of NSCLC adenocarcinoma in the United States and occur more frequently in nonsmokers and younger patients. In advanced-stage NSCLC, the presence of an ALK translocation strongly predicts for sensitivity to ALK TKIs (eg, crizotinib, ceritinib, alectinib) (L. Sequist & Neal, 2017).

ROS1 - is a receptor tyrosine kinase that acts as a driver oncogene in 1 to 2 percent of NSCLC via a genetic translocation between ROS1 and other genes, the most common of which is CD74 (Bergethon et al., 2012). Histologic and clinical features that are associated with ROS1 translocations include adenocarcinoma histology, younger patients, and never-smokers. The ROS1 tyrosine kinase is highly sensitive to crizotinib due to a high degree of homology between the ALK and ROS tyrosine kinase domains (L. Sequist & Neal, 2017)

HER2 (ERBB2) is an EGFR family receptor tyrosine kinase. Mutations in HER2 have been detected in approximately 1 to 2 percent of NSCLC tumors (Arcila et al., 2012). They usually involve small in-frame insertions in exon 20, but point mutations in exon 20 have also been observed. These tumors are predominantly adenocarcinomas, are more prevalent among never-smokers, and a majority of these patients are women. There is no obvious association between HER2 amplification and HER2 mutations, and previous trials demonstrated no benefit for trastuzumab in HER2-amplified NSCLC. This testing is not recommended in NSCLC (L. Sequist & Neal, 2017; Zinner et al., 2004)

BRAF mutation — BRAF is a downstream signaling mediator of KRAS that activates the mitogen-activated protein kinase (MAPK) pathway. Activating BRAF mutations have been observed in 1 to 3 percent of NSCLC and are usually associated with a history of smoking (L. V. Sequist, Heist, et al., 2011). BRAF inhibition with oral small-molecule TKIs (e.g., vemurafenib and dabrafenib) appears to be an effective strategy in the treatment of progressive BRAF V600-mutant NSCLC (L. Sequist & Neal, 2017)

MET abnormalities — MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF). MET abnormalities include MET exon 14 skipping mutations (in 3 percent of lung adenocarcinomas and up to 20 percent of pulmonary sarcomatoid carcinomas), MET gene amplification (in 2 to 4 percent of treatment naïve NSCLC), and MET and EGFR co-mutations (in 5 to 20 percent of EGFR-mutated tumors that have acquired resistance to EGFR inhibitors) (Liu et al., 2016; Okuda, Sasaki, Yukiue, Yano, & Fujii, 2008; L. Sequist & Neal, 2017)

RET translocation — The RET gene encodes a cell surface tyrosine kinase receptor that is frequently altered in medullary thyroid cancer. Recurrent translocations between RET and various fusion partners (CCDC6, KIF5B, NCOA4) have been identified in 1 to 2 percent of adenocarcinomas, and occur more frequently in younger patients and in never-smokers (L. Sequist & Neal, 2017; Takeuchi et al., 2012; Wang et al., 2012)

RAS mutations — Activating KRAS mutations are observed in approximately 20 to 25 percent of lung adenocarcinomas in the United States and are generally associated with smoking (O’Byrne et al., 2011). The presence of a KRAS mutation appears to have at most a limited effect on overall survival in patients with early-stage NSCLC (Shepherd et al., 2013), although some older data had suggested that it was associated with a worse prognosis (Mascaux et al., 2005). NRAS is homologous to KRAS, associated with smoking, and mutations have been observed in approximately 1 percent of NSCLC (L. V. Sequist, Heist, et al., 2011). The clinical significance of NRAS mutations is unclear, and no effective targeted therapies have been identified (L. Sequist & Neal, 2017).

PIK3CA, AKT1, PTEN alterations — PIK3CA encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which is an intracellular central mediator of cell survival signals. AKT1 acts immediately downstream of PI3K. Phosphatase and tensin homolog (PTEN) inhibits AKT by dephosphorylation.
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Oncogenic alterations in this pathway, which occur more frequently in tumors of squamous histology and smokers, include gain-of-function mutations in PIK3CA and AKT1, and loss of PTEN function (Jin et al., 2010; Lee et al., 2010). PIK3CA mutations may also promote resistance to EGFR TKIs in EGFR-mutant NSCLC (L. V. Sequist, Waltman, et al., 2011). Small-molecule inhibitors of PI3Kinase and AKT are in clinical development and hold particular hope for the treatment of squamous cell lung cancer. However, since these alterations often overlap with other molecular changes, they may represent a "passenger" mutation rather than a "driver" alteration, and therefore clinical efficacy of these agents against specific molecular alterations is unknown.

Precision oncology is now the evidence-based standard of care for the management of many advanced NSCLCs. Expert consensus has defined minimum requirements for routine testing and identification of epidermal growth factor (EGFR) mutations (15% of tumors harbor EGFR exon 19 deletions or exon 21 L858R substitutions) and anaplastic lymphoma kinase (ALK) rearrangements (5% of tumors) in advanced lung adenocarcinomas (ACs). Application of palliative targeted therapies with oral tyrosine kinase inhibitors (TKIs) in advanced/metastatic lung ACs harboring abnormalities in EGFR (gefitinib, erlotinib, afatinib) and ALK/ROS1/MET (crizotinib) has consistently led to more favorable outcomes compared with traditional cytotoxic agents (Shea, Costa, & Rangachari, 2016).

State and Federal Regulations, as applicable

The FDA has approved the following tests for Non-Small Cell Lung Cancer:

- Cobas EGFR Mutation Test v2    Roche Molecular Systems, Inc.
- Therascreen EGFR RGQ PCR Kit    Qiagen Manchester Ltd
- Oncomine Dx Target Test                   Life Technologies Corp

Guidelines and Recommendations

The NCCN (2018) recommends molecular testing before any systemic therapy, specifically for advanced or metastatic non squamous NSCLC or NSCLC NOS to assess a minimum of EGFR mutations, BRAF mutations, ALK rearrangements, and ROS1 rearrangements. Testing for ALK rearrangements and EGFR mutations can be considered in select patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported.

The 2018 CAP (Lindeman et al., 2018) recommendations were updated to include “3 categories into which genes should be placed. 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. All other genes are considered investigational at the time of publication.”

They elaborate to recommend: “In this context, institutions providing care for lung cancer patients have a choice: (1) offer a comprehensive cancer panel that includes all of the genes in the first 2 categories (EGFR, ALK, ROS1, BRAF, MET, ERBB2 [HER2], KRAS, RET) for all appropriate patients, or (2) offer targeted testing for the genes in the must-test category (EGFR, ALK, ROS1) for all appropriate patients and offer as a second test an expanded panel containing the second-category genes (BRAF, MET, ERBB2 [HER2], and RET) for patients who are suitable candidates for clinical trials, possibly after performing a single-gene KRAS test to exclude patients with KRAS-mutant cancers from expanded panel testing.”

PD-L1 receptor expression

Monoclonal antibody therapy (human immune-checkpoint- inhibitor antibodies that inhibit PD-1 receptors or PD-L1) have been developed to treat individuals with non-small cell lung cancer. The National Comprehensive Cancer Network recommends this testing prior to first-line treatment with the monoclonal antibody therapy, pembrolizumab in patients with metastatic NSCLC with negative or
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unknown test results for EGFR mutations, BRAF mutations, ALK rearrangements, and ROS1 rearrangements. PD-L1 expression is the best biomarker to assess individuals with non-small cell lung cancer for use of the monoclonal antibody therapy, pembrolizumab.

In 2017, American Society of Clinical Oncology (ASCO) published a clinical practice guideline update on systemic therapy for Stage IV NSCLC (Hanna et al, 2017). ASCO recommended that “Regarding first-line treatment for patients with non–squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK/ROS1), if the patient has high programmed death ligand 1 (PD-L1) expression, pembrolizumab should be used alone; if the patient has low PD-L1 expression, clinicians should offer standard chemotherapy. Regarding second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy, if NSCLC tumor is positive for PD-L1 expression, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab; if tumor has negative or unknown PD-L1 expression, clinicians should use nivolumab or atezolizumab (Hanna et al., 2017).”

EGFR Gene

The National Comprehensive Cancer Network (NCCN) recommended testing for EGFR mutations of NSCLC tumors that are adenocarcinoma, large cell, or NSCLC not otherwise specified (Category 1). The NCCN also indicates that EGFR mutation testing should be considered in individuals with squamous cell carcinoma, in those who have never smoked, small biopsy specimens, and those with mixed histology (Category 2A).

The 2017 NCCN guidelines on NSCLC stated that gefitinib was recently re-approved by FDA. Erlotinib (category 1), afatinib (category 1), or gefitinib (category 1) are recommended as first-line systemic therapy in patients with sensitizing EGFR mutations.

The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology (CAP/IASLC/AMP) guidelines indicate that “EGFR molecular testing should be used to select patients for EGFR- targeted tyrosine kinase inhibitor therapy (Evidence Grade: A)” (Lindeman et al, 2013). Testing is recommended for adenocarcinomas and mixed lung cancers “regardless of histologic grade.” However, in the setting of fully excised lung cancer specimens, EGFR testing is not recommended for lung cancer without any adenocarcinoma component (Evidence Grade: A). In the setting of more limited lung cancer specimens where an adenocarcinoma component cannot be completely excluded, EGFR testing is recommended “in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing” (Evidence Grade: A). The 2018 CAP guidelines (Lindeman et al., 2018) reaffirmed the 2013 guideline recommendations of universal testing of lung cancer patients with advanced-stage cancers with an adenocarcinoma component, using molecular diagnosis for activating “hot-spot” mutations in EGFR exons 18 to 21 with at least 1% prevalence (ie, codons 709 and 719, exon 19 deletion 768, and exon 20 insertions 790, 858, and 861).

In 2018 CAP also added the recommendation that: “In lung adenocarcinoma patients who harbor sensitizing EGFR mutations and have progressed after treatment with an EGFR-targeted tyrosine kinase inhibitor, physicians must use EGFR T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy. Laboratories testing for EGFR T790M mutation in patients with secondary clinical resistance to EGFR targeted kinase inhibitors should deploy assays capable of detecting EGFR T790M mutations in as little as 5% of viable cells.”

The American Society of Clinical Oncology (ASCO) recommends testing for EGFR mutations in tumors of NSCLC patients who “are being considered for first-line therapy with an EGFR TKI” to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy (Keedy et al, 2011). In 2014, ASCO endorsed the CAP/IASLC/AMP guidelines and highlighted three evolving areas: advances in ALK testing methodology, considerations for selecting appropriate populations for molecular testing, and emergence of other targetable molecular alterations (Leighl et al, 2014).

The package inserts for both erlotinib and afatinib indicate that they are for “first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor
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receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

**ALK Gene**

NCCN (v.4.2015) states that ALK rearrangement testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified, because crizotinib (category 1) is recommended for patients who are positive for ALK rearrangements. If ALK-positive status is discovered before first-line chemotherapy, give crizotinib (category 1), or if ALK rearrangement is discovered during first-line chemotherapy, interrupt or complete planned chemotherapy and start crizotinib. If there is progression on crizotinib, NCCN guidelines recommend multiple options (category 2A) including continuing crizotinib, switching to ceritinib, and considering local therapies depending on symptoms.

The 2018 NCCN guidelines (version 3.2018) on NSCLC recommended use alectinib as the preferred first-line treatment for ALK-positive metastatic NSCLC (Category 1). Crizotinib and ceritinib are also recommended as first line therapies for patients with ALK rearrangements. The guidelines also state that testing for ALK rearrangements can be considered in patients with squamous cell histology if they are never smokers, or have mixed histology, or when the biopsy specimen is small (Category 2A).

The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines indicate that “ALK molecular testing should be used to select patients for ALK-targeted TKI therapy (Evidence Grade: B)” (Lindeman et al, 2013). Testing is recommended for adenocarcinomas and mixed lung cancers “regardless of histologic grade.” However, in the setting of fully excised lung cancer specimens, ALK testing is not recommended for lung cancer without any adenocarcinoma component (Evidence Grade: A). In the setting of more limited lung cancer specimens where an adenocarcinoma component cannot be completely excluded, ALK testing is recommended “in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing” (Evidence Grade: A).

In 2018 CAP (Lindeman et al., 2018) added the recommendation that “IHC is an equivalent alternative to FISH for ALK testing”, and that “although at the time of writing RT-PCR and NGS are not approved by the FDA in the United States as first-line methods for determining ALK status in selection of patients for ALK inhibitor therapy, these approaches have shown comparable performance with IHC when designed to detect the majority of fusions, and are standard practice in many other countries. These methods are highly specific for most fusions, and patients with positive results should be treated with an ALK inhibitor, although patients with negative results may benefit from a more sensitive method to exclude the possibility of a variant fusion. Similarly, amplicon-based NGS assays of DNA may likewise fail to detect all fusion variants, and therefore a capture-based DNA or RNA approach is preferred for NGS testing for ALK fusions. Current data are still too limited to develop a specific recommendation either for or against the use of NGS for ALK fusions as a sole determinant of ALKTKI therapy”

Lastly the CAP found that “There is currently insufficient evidence to support a recommendation for or against routine testing for ALK mutational status for lung adenocarcinoma patients with sensitizing ALK mutations who have progressed after treatment with an ALK-targeted tyrosine kinase inhibitor.”

**KRAS Gene**

The National Comprehensive Cancer Network (2018) guidelines note that “The KRAS oncogene is a prognostic biomarker of poor survival for patients with NSCLC when compared to the absence of KRAS mutations, independent of therapy. KRAS mutations are also predictive of lack of benefit from EGFR TKI therapy. EGFR, KRAS, ROS1, ad ALK genetic alterations do not usually overlap.” “KRAS testing may identify patients who may not benefit from further molecular testing. Targeted therapy is not currently available for patients with KRAS mutations, although immune checkpoint inhibitors appear to be effective; MEK inhibitors are in clinical trials.
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The 2018 College of American Pathology (Lindeman et al., 2018) recommendations were updated to state that “KRAS molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include KRAS as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative.”

According to the European Society for Medical Oncology (ESMO), genetic alterations, which are key oncogenic events (driver mutations), have been identified in NSCLC, with two of these—EGFR mutations and the anaplastic lymphoma kinase (ALK) rearrangements—determining approved, selective pathway-directed systemic therapy. The ESMO guidelines do not specifically mention KRAS mutation testing (Novello et al., 2016).

**BRAF Gene**

The NCCN Panel (2018) recommends testing for BRAF mutations based on data showing the efficacy and FDA approval of dabrafenib/trametinib for patients with BRAF V600 mutations.

The 2018 CAP recommendations (Lindeman et al., 2018) state: “BRAF molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include BRAF as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative.”

**ROS1 Gene**

In the 2017 guidelines on NSCLC, the NCCN panel recommended testing for ROS1 gene rearrangement for patients with nonsquamous NSCLC or NSCLC not otherwise specified (Category 2A). The guidelines also state that testing for ROS1 rearrangements can be considered in patients with squamous cell histology if they are never smokers, or have mixed histology, or when the biopsy specimen is small (Category 2A). Crizotinib is recommended for patients with ROS1 rearrangements.

The 2018 CAP (Lindeman et al., 2018) recommendations state: “ROS1 testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics. ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.

**Other Genes**

NCCN does not give specific recommendations for testing for genetic alterations in the genes RET, MET, or HER2 in NSCLC. However, they “strongly advise broader molecular profiling to identify rare driver mutations to ensure that patients receive the most appropriate treatment”. The following targeted agents are recommended for patients with specific genetic alterations: MET: crizotinib (category 2A); RET rearrangements: cabozantinib, vandetanib (category 2A); HER2 mutations: ado-trastuzumab emtansine (category 2A).

The CAP 2018 recommendations state that RET, MET and ERBB (HER2) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include RET, MET, or ERBB (HER2) as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative.

**Microsatellite Instability**

In May 2017, the U.S. Food and Drug Administration granted accelerated approval for use of pembrolizumab in individuals with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Tumors with these biomarkers are found most commonly in endometrial, colorectal, and gastrointestinal cancers, but can appear in other solid tumors. This indication would cover patients with Non-Small Cell lung cancer tumors that have progressed despite prior treatment and for whom no alternative treatment is available (Boyiadzis et al., 2018; Lemery, Keegan, & Pazdur, 2017; Ratner &
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Lennerz, 2018). “This is the first example of a tissue-agnostic FDA approval of a treatment based on a patient’s tumor biomarker status, rather than on tumor histology (Boyiadzis et al., 2018).”

Broad Molecular Profiling for Biomarkers

The NCCN recommends that biomarker testing be done as part of broad molecular profiling to minimize wasting of tissue with validated test that assases a minimum of EGFR mutations, BRAF mutations, ALK rearrangements, and ROS1 rearrangements.

The CAP recommends (Lindeman et al., 2018) that “Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1.” They found that “NGS enables the simultaneous assessment of all 3 of the “must-test” genes in lung cancer—EGFR, ALK, ROS1—as well as each of the genes suggested for inclusion in larger panels—BRAF, RET, ERBB2 (HER2), KRAS, MET—and hundreds to thousands of other genes that may have potential roles in cancer development. In addition to small mutations, NGS assays are able to detect fusions/rearrangements and copy number changes in the targeted genes, if designed with these alterations in mind. Numerous studies have demonstrated the excellent sensitivity of NGS methods relative to single-gene targeted assays, particularly for single-nucleotide–substitution mutations. Next-generation sequencing methods typically require less input DNA and can accommodate smaller samples with lower concentrations of malignant cells, and, although typically slower than 1 single-gene assay, can often be performed more rapidly than sequential multiple single-gene assays. A reduced need for repeat biopsy is an additional benefit of panel testing.”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81210, 81235, 81275, 81276, 81301, 81401, 81404, 88271, 88272, 88273, 88342, 88360, 88361

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Medical Director review 8/2019


Medical Director review 3/2020

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for testing for targeted therapy of non-small-cell lung cancer when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Extensive revisions to “When Covered” section: Reordered and reworded indications, new statements for #2, 4, 5. Added note: For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162
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Reimbursement Policy. Deleted coding table from Billing/Coding section and deleted CPT codes 81445, 81450, 81455. Medical Director review 8/2019. (lpr)

10/29/19  Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

2/11/20  Reviewed by Avalon Q4 2019 CAB. Removed CPT 81538 from Billing/Coding section. Under “When Covered” section added entrectinib to statement “Testing for NTRK gene is considered medically necessary for individuals with metastatic or advanced NSCLC before first-line or subsequent therapy with larotrectinib or entrectinib. Medical Director review 2/2020. (lpr)

5/12/20  Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.