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

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Line(s) of Business: HMO; PPO; QUEST Integration	**Precertification:** Refer to the GTM Utilization Review Matrix

I. Policy Description

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. 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.

For guidance concerning the use of circulating tumor cells (i.e. liquid biopsy) in NSCLC, please refer to the Liquid Biopsy medical policy.

For guidance concerning Tumor Mutational Burden Testing (TMB) and/or Microsatellite instability (MSI) analysis please refer to the Microsatellite Instability and Tumor Mutational Burden Testing medical policy.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) Using a validated test, molecular profiling to identify all of the established actionable driver mutations (*ALK*, *BRAF*, *EGFR*, *ERBB2(HER2), KRAS*, *METex14* skipping, *NTRK 1/2/3*, *RET*, *ROS1)* **MEETS COVERAGE CRITERIA** and is recommended.
2) Testing for *BRAF, EGFR,* and/or *MET* mutations before any systemic therapy initiation in patients with non-Small Cell Lung Cancer (NSCLC) **MEETS COVERAGE CRITERIA**.
3) Testing for *ALK*, *RET,* and/or *ROS1* rearrangements before any systemic therapy initiation in patients with NSCLC **MEETS COVERAGE CRITERIA**.
4) Testing for *NTRK1/2/3* gene fusions **MEETS COVERAGE CRITERIA** for individuals with NSCLC before first-line or subsequent targeted therapy
5) To direct therapy in patients with NSCLC, analysis of PD-L1 expression by immunohistochemistry **MEETS COVERAGE CRITERIA**.
6) *KRAS* molecular testing **DOES NOT MEET COVERAGE CRITERIA** as a routine stand-alone assay and as a sole determinant of targeted therapy.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

7) Analysis of PD-L1 expression by immunohistochemistry in all other situations **DOES NOT MEET COVERAGE CRITERIA**.
8) As a stand-alone assay and as a sole determinant of targeted therapy, analysis of a variant of uncertain significance (VUS), even if the VUS occurs in a gene in which other variants are clinically actionable, **DOES NOT MEET COVERAGE CRITERIA**.
9) To direct targeted therapy in patients with NSCLC, analysis for genetic alterations in genes not mentioned above **DOES NOT MEET COVERAGE CRITERIA.**

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.

III. Table of Terminology

Term	Definition
AKT1	*AKT serine/threonine kinase 1 gene*
ALK	*Anaplastic lymphoma kinase*
AMP	Association for Molecular Pathology
ARMS	Amplification Refractory Mutation System
ASCO	American Society of Clinical Oncology
BRAF	*B-Raf proto-oncogene serin/threonine kinase gene*
CAP	College Of American Pathologists
CD74	*Cluster of Differentiation 74*
cfDNA	Cell-free deoxyribose nucleic acid
CGP	Comprehensive genomic profiling
CLIA	Clinical Laboratory Improvement Amendment Of 1988
CMS	The Centers for Medicare and Medicaid
CNS	Central nervous system
DCB	Durable clinical benefit
DNA	Deoxyribose nucleic acid
EGFR	*Epidermal Growth Factor Receptor gene*
ERBB2	*Erythroblastic oncogene B*
ERBB2(HER2)	*Erythroblastic oncogene B (Human epidermal growth factor receptor 2)*
ESMO	European Society for Medical Oncology
FBXW7	*F-Box and WD repeat domain containing 7*
FDA	Food and Drug Administration
FIG	Fused in glioblastoma
FISH	Fluorescence in situ hybridization
HER	Electronic health records
HER2	*Human epidermal growth factor receptor 2*

HGF	Hepatocyte growth factor
IASLC	International Association for the Study of Lung Cancer
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
KRAS	*Kirsten rat sarcoma viral oncogene homolog*
LDTs	Laboratory-developed tests
MAPK	Mitogen-activated protein kinase
MET	*MET Proto-Oncogene, Receptor Tyrosine Kinase*
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NDB	No durable benefit
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
NTRK	*Neurotrophic tyrosine receptor kinase gene*
OH	Ontario Health
PBRM1	*Protein Polybromo-1 gene*
PCR	Polymerase chain reaction
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI3K	Phosphatidyl 3-kinase (Pi3K)
PIK3CA	*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha gene*
PTEN	*Phosphatase and TENsin homolog deleted on chromosome 10 gene*
pts	Patients
RAS	*Rat sarcoma virus gene*
RET	*Rearranged during transfection gene*
ROS1	*ROS proto-oncogene 1*
RT-PCR	Real-time polymerase chain reaction
SCLC	Small-cell lung cancer
SETD2	*SET Domain Containing 2, Histone Lysine Methyltransferase*
STK11	*Serine/threonine kinase 11 gene*
TMB	Tumor mutational burden
TP53	*Tumor protein p53 gene*
TSC2	*TSC complex subunit 2 gene*

IV. Scientific Background

Primary lung cancer is one of the most common malignancies. In the United States, approximately 236,740 individuals are diagnosed and more than 130,180 deaths occur annually. Approximately 95% of lung cancers are either non-small cell or small cell, and 80%-85% are non-small cell lung cancers (NSCLC). Specific molecular treatments for patients based on certain genetic mutations have been developed. Currently, *EGFR*-, *ALK*-, *ROS1*-, *BRAF*-, and *NTRK*-positive cases of NSCLC have FDA-approved targeted therapies (i.e. specific treatments for specific mutations), whereas *HER2*-, *MET*-, and *RET*-positive cases are treated with off-label therapies. Therapies for other mutations such as *RAS, PTEN, AKT1*, and *PIK3CA* mutations are currently in development. Still, other genetic biomarkers, such as PD-L1 expression and microsatellite instability (MSI) testing may contribute to the management of NSCLC cases.

EGFR tyrosine kinase mutations are observed in approximately 15% of NSCLC adenocarcinoma cases in the United States and occur more frequently in nonsmokers. The presence of an *EGFR* mutation usually confers a better prognosis and may be treated by *EGFR* tyrosine kinase inhibitors (TKIs) such as erlotinib. *ALK* tyrosine kinase translocations are present in approximately 4% of NSCLC adenocarcinoma cases in the United States and occur more frequently in nonsmokers and younger patients. In advanced-stage NSCLC, the presence of an *ALK* translocation may be treated by *ALK* TKIs such as crizotinib. Other effective TKIs include ceritinib, alectinib, brigatinib, and lorlatinib. Studies have indicated that treatment with these therapeutic TKIs significantly prolongs progression-free survival.

ROS1 is a receptor tyrosine kinase that acts as a driver oncogene in 1 to 2% of NSCLC cases by a translocation between *ROS1* and other genes such as *CD74*. *ROS1* translocations are usually associated with younger patients and individuals who have never smoked tobacco. Since the *ALK* and ROS tyrosine kinases are significantly homologous, the *ROS1* tyrosine kinase is treatable by *ALK* TKIs such as crizotinib. *HER2 (ERBB2)* is an *EGFR* family receptor tyrosine kinase. Mutations in *HER2* have been detected in approximately 1 to 3% of NSCLC tumors. These mutations are most frequent in exon 20, resulting primarily in adenocarcinomas. This mutation is more prevalent among individuals who have never smoked tobacco and women.

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% of NSCLC cases and are usually associated with smokers. *BRAF* inhibition with oral small-molecule TKIs has been used to treat this version of NSCLC.
MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF). MET mutations include *MET* exon 14 skipping, *MET* gene amplification, and *MET* and *EGFR* co-mutations. Tepotinib has shown evidence of promise in treating *MET*-exon 14 skipping cases. Crizotinib, an *ALK*/ROS inhibitor, has also been used to treat MET-exon 14 skipping cases of NSCLC. Other MET-specific therapies are under investigation such as glesatinib and savolitinib. For those with *MET* amplification, capmatinib or crizotinib are suggested lines of treatment, but are not yet approved for this indication by the FDA and continue to be a line of active research.

The *RET* gene encodes a cell surface tyrosine kinase receptor that may be translocated in adenocarcinomas. These mutations occur more frequently in younger patients and in individuals who have never smoked tobacco. Off-label *RET* inhibitors, such as alectinib, have been used to treat RET-positive cases of NSCLC. In addition, the FDA has approved selpercatinib and pralsetinib for advanced NSCLC in adult patients.

RAS mutations, in either *KRAS* or *NRAS,* are associated with NSCLC. Activating *KRAS* mutations have been observed in approximately 20 to 25% of lung adenocarcinomas in the United States and are generally associated with smoking. The presence of a *KRAS* mutation has a limited effect on overall survival in patients with early-stage NSCLC. *NRAS* is homologous to *KRAS* and associated with smoking as well; however, NRAS mutations comprise only 1% of NSCLC cases. The clinical significance of *NRAS* mutations is unclear, and no effective targeted therapies exist at this time.

PIK3CA, *AKT1*, and *PTEN* are three genes involved in the same pathway. *PIK3CA* encodes the catalytic subunit of phosphatidyl 3-kinase (PI3K), AKT1 acts immediately downstream of PI3K, and phosphatase and tensin homolog (PTEN) inhibits AKT by dephosphorylation. Oncogenic alterations in this pathway include gain-of-function mutations in *PIK3CA* and *AKT1*, and loss of PTEN function. *PIK3CA* mutations may also cause resistance to *EGFR* TKIs in *EGFR*-mutated NSCLC. Small-molecule inhibitors of PI3K and AKT are being developed, but clinical efficacy of these agents against specific molecular alterations is unknown.

Other genetic biomarkers include PD-L1 assessment and microsatellite instability (MSI) testing. Programmed death-1 ligand (PD-L1) expression testing via immunohistochemistry (IHC) is used to guide therapy for patients with NSCLC. Tumor cells present PD-L1 to T-cells to inhibit the immune response by downregulating cytokine production and T-cell proliferation, thereby allowing these tumor cells to evade immune system activity. Monoclonal antibody therapy (immune therapy) has been developed to inhibit this pathway and overcome this mechanism of immune system evasion (Teixidó, Vilariño, Reyes, & Reguart, 2018). Tumor PD-L1 protein expression through immunohistochemistry can be ordered to pinpoint first-line treatment options for NSCLC outside of chemotherapy.
Microsatellites are short tandem repeat sequences located throughout the genome. However, these sequences are subject to instability caused by faulty mismatch repair genes. This has historically been reported in other cancers, such as Lynch syndrome, and has been reported in NSCLC. MSI testing may be used to evaluate NSCLC cases.

Precision oncology is now the evidence-based standard of care for the management of many advanced NSCLCs. Expert consensus guidelines have defined minimum requirements for routine testing and identification of *EGFR* and *ALK* mutations in advanced lung adenocarcinomas. Targeted use of TKIs based on certain genetic mutations has consistently led to more favorable outcomes compared with traditional cytotoxic agents. The concept of targeted testing has been approved by the FDA, as package inserts for drugs such as erlotinib specify used for *EGFR* mutations and other drugs such as pembrolizumab have gained approval for specific types of tumors (in this case, high-MSI tumors). Proprietary tests are available for identification of relevant mutations, including larger genetic panels. FoundationOne's 324-gene panel and Oncomine's 23-gene panel are both FDA-approved as companion diagnostics for non-small cell lung cancer targeted therapies. Recently, Guardant 360 CDx was FDA-approved for use as a companion diagnostic to identify NSCLC patients with *EGFR* mutations who may benefit from Tagrisso (osimertinib). The company Cobas has a diagnostic approved to identify patients with metastatic NSCLC who might benefit from Tarceva® (erlotinib) based on formalin-fixed tissue preparation to identify *EGFR* mutation; a Cobas assay was also FDA approved as a companion diagnostic using liquid biopsy and circulating-free tumor DNA.

Clinical Utility and Validity

Lin et al. (2017) evaluated the association between *EGFR* and *EGFR*-TKI efficacy in stage IV NSCLC patients. In this study, 94 patients were assessed. The authors calculated a 74.5% objective response rate and a 97.9% disease control rate for *EGFR*-TKI treatment. The authors concluded that *EGFR*-TKI therapy resulted in survival benefits for *EGFR*-mutant patients regardless of "gender, smoking history, pathologic type, type of *EGFR* mutations, brain metastasis and timing of targeted therapy".

Li et al. (2017) examined the effect of number of *EGFR* mutations on the efficacy of *EGFR* TKIs. In this study, 201 patients with *EGFR* mutations were evaluated. These patients were quantitatively separated into "low" and "high" groups based on "amplification refractory mutation system (ARMS) method optimized with competitive blockers and specific mutation quantitation (ARMS+)." The cutoff value was determined by a receiving operating characteristic analysis in a training group and further validated in another group. The investigators found the median progression-free survival (PFS) to be 15 months in the high group compared to two months in the low group. Similar results were reported in the validation group. The authors concluded that the abundance of *EGFR* mutations was significantly associated with objective response to *EGFR* TKIs. However, they also noted the abundance of *EGFR* T790M mutation may adversely affect PFS rather than objective response rate.

Wang et al. (2017) investigated the effect of *ALK* rearrangements on NSCLC patients. The authors reviewed 15 studies including 4981 patients. The study found that *ALK* positive (*ALK*+) patients faced better prognoses (hazard ratio 0.81 of *ALK* negative patients) except in the non-smoking population (hazard ratio 1.65). *ALK*+ patients also experienced a significantly higher objective response rate in pemetrexed-based chemotherapy, but not with *EGFR*-TKI treatment.

Gainor et al. (2016) performed a study evaluating the efficacy of PD-L1 blockades on *EGFR* and *ALK* positive patients. The study evaluated 58 patients; 28 had an *EGFR* or *ALK* mutation whereas 30 were wild-type. The investigators found only one of the 28 patients (3.6%) with either mutation had an objective response whereas seven of the 30 (23.3%) wild-type patients had an objective response.
Planchard et al. (2016) evaluated the efficacy of the FDA-approved combination of da*BRAF*enib plus trametinib on previously treated *BRAF*-mutant metastatic NSCLC. The study included 57 patients; 36 of these patients achieved an overall response. However, serious adverse events were reported in 32 of these patients. The authors concluded that this combination may represent a robust therapy with a management safety profile in *BRAF*-positive NSCLC patients.

A 2019 comprehensive study by Singal and associates (2019) examined the electronic health records (EHR) of 4064 individuals with NSCLC from 275 different oncology practices to explore "associations between tumor genomics and patient characteristics with clinical outcomes." They note that 21.4% of these individuals had a mutation in *EGFR*, *ALK*, or *ROS1*, and that patients with driver mutations who had targeted therapies had significantly improved overall survival times than individuals who did not have targeted therapies (median of 18.6 versus 11.4 months, respectively); moreover, a tumor mutational burden (TMB) of 20 or higher was associated with improved overall survival for patients on PD-L1-targeted therapy than those patients with a TMB less than 20. The authors concluded that they replicated similar associations from previous research "between clinical and genomic characteristics, between driver mutations and response to targeted therapy, and between TMB and response to immunotherapy".

Siena et al. (2019) reported integrated data from three clinical trials focusing on entrectinib. Patients had either *ROS1*-driven or *NTRK*-driven cases of NSCLC. Out of 53 patients with *ROS1* mutations, approximately 80% responded to entrectinib. Out of 54 patients with *NTRK* mutations, approximately 60% responded. The authors considered entrectinib to be "tolerable with a manageable safety profile", and concluded that "entrectinib induced clinically meaningful durable responses in [patients] with *ROS1*+ NSCLC or *NTRK*+ solid tumors with or without CNS disease".

Alborelli et al. (2020) investigated the predictive power of tumor mutational burden (TMB) for patients treated with immune checkpoint inhibitors (ICIs). The study included 76 NSCLC patients treated with ICIs. TMB was evaluated with the "Oncomine™ Tumor Mutational Load" sequencing assay. Patients were separated into cohorts of "durable clinical benefit" (DCB) or "no durable benefit" (NDB). TMB was found to be higher in the DCB cohort (median TMB of 8.5 mutations / Mb compared to 6 mutations / Mb in NDB). 64% of patients in the highest tertile of TMB were responders, compared to 33% and 29% in the middle and lowest tertiles, respectively. TMB-high patients were also found to have higher progression free survival and overall survival. Overall, the authors concluded that the TML panel was an effective tool to stratify patients for ICI treatment and suggested that "a combination of biomarkers might maximize the predictive precision for patient stratification." Further, the authors remarked that their data "supports TMB evaluation through targeted NGS in NSCLC patient samples as a tool to predict response to ICI therapy".

Volckmar et al. (2019) assessed the "feasibility and clinical utility of comprehensive, NGS-based genetic profiling for routine workup of advanced NSCLC." The authors based their study on the first 3000 patients seen in their facility. Of the patients tested, the authors identified 807 patients eligible for "currently approved, *EGFR-/BRAF-/ALK*- and *ROS1*-directed therapies," while 218 additional cases with *MET*, *ERBB2* (*HER2*) and *RET* alterations could "potentially benefit from experimental targeted compounds." Other co-mutations such as *TP53* and *STK11* were also frequently identified, which may be potentially useful predictive and prognostic tools. The authors also noted logistical successes, such as reliability, low dropout rate, fast turnaround times, and minimal tissue requirements. Overall, the authors concluded that this diagnostic approach demonstrated "practicability in order to support individualized decisions in routine patient care, enrollment in molecularly stratified clinical trials, as well as translational research".

Signorovitch et al. (2019) aimed to evaluate the "budget impact of increased use of CGP [comprehensive genomic profiling] using a 324-gene panel (FoundationOne) vs non-CGP (represented by a mix of conventional molecular diagnostic testing and smaller NGS hotspot panels) and the number needed to test with CGP to gain 1 life year." The authors developed a decision analytic model to assess the financial impact of increased CGP in advanced non-small cell lung cancer (NSCLC). The study included two million covered lives, of which 532 had advanced NSCLC. Of these patients, 266 underwent molecular diagnostic testing. An increased in CGP among those tested (from 2%-10%) was associated with a $0.02 per member per month budget impact, of which $0.013 "was attributable to costs of prolonged drug treatment and survival and $0.005 to testing cost." Overall, the addition of one life year was met with 12 patients tested. The authors concluded that a 2%-10% increase in CGP use was associated with a "modest budget impact, most of which was attributed to increased use of more effective treatment and prolonged survival".

In a prospective study, Peled et al. (2020) investigated the clinical utility of early cell-free deoxyribose nucleic acid (cfDNA) analysis using Guardant 360 CDx in treatment-naive NSCLC patients. Ten patients were studied and the median time from blood draw to receiving the cfDNA results was nine days. Actionable biomarkers were identified in four of the ten patients by both biopsy analysis and cfDNA analysis. Overall, three patients received biomarker-based treatment (one osimertinib, one alectinib, and one crizotinib). The authors concluded that "cfDNA analysis should be ordered by the pulmonologists early in the evaluation of patients with NSCLC, which might complement the tumor biopsy".

Al-Ahmadi et al. (2021) studied the overall impact and racial differences of NGS testing in NSCLC patients. The study tested 295 patients with Stage IV NSCLC using the FoundationOne assay and genomic differences were compared by race. "Patients undergoing NGS testing had significantly longer survival of 25.3 months versus those who did not undergo sequencing with a median survival of 14.6 months (P=.002) irrespective if they received targeted therapy or not." In addition, there was no difference in NGS results based on race. However, African American patients had a higher rate of mutations in *PBRM1, SETD2, TSC2*, and *FBXW7*. Overall, there is no racial difference in NGS utilization and testing does increase survival.

Boeckx et al. (2020) convened a small study of 46 never-smoking, non-small cell lung cancer (NSCLC) patients to investigate genomic alterations in non-smoking individuals. There are few genomic studies focused primarily on this subgroup of patients with NSCLC who have never smoked. Whole exome and low-coverage whole genome sequencing was performed on tumors and matched germline DNA. Fewer somatic mutations, genomic breakpoints, and a smaller percentage of the genome with chromosomal instability in lung tumors were observed in non-smokers compared to smokers. In addition, TSC22D1 was noted as a potential driver gene of NSCLC. The frequency of mutation of TP53, which is associated with negative long-term outcomes, was lower in those who were never-smokers than in smokers. That said, they found driver genes such as EGFR and ERBB2, as well as amplifications in MET were higher in never-smokers. The authors concluded there was a "more favorable prognosis for never smokers with NSCLC".

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

In the version 2.2022 update of the NCCN guidelines for NSCLC released on 3/07/2022, they state, "Numerous gene alterations have been identified that impact therapy selection. Testing of lung cancer specimens for these alterations is important for identification of potentially efficacious targeted therapies, as well as avoidance of therapies unlikely to provide clinical benefit". The NCCN states, "Appropriate possible testing methodologies are indicated below for each analyte separately; however, several methodologies are generally considerations for use:

- Next-generation sequencing (NGS) is used in clinical laboratories. Not all types of alterations are detected by individual NGS assays and it is important to be familiar with the types of alterations identifiable in individual assays or combination(s) of assays.
- It is recommended at this time that when feasible, testing be performed via a broad, panel-based approach, most typically performed by next generation sequencing (NGS). For patients who, in broad panel testing don't have identifiable driver oncogenes (especially in never smokers), consider RNA-based NGS if not already performed, to maximize detection of fusion events…
- Real-time polymerase chain reaction (PCR) can be used in a highly targeted fashion (specific

mutations targeted). When this technology is deployed, only those specific alterations that are targeted by the assay are assessed.

- Sanger sequencing requires the greatest degree of tumor enrichment. Unmodified Sanger sequencing is not appropriate for detection of mutations in tumor samples with less than 25% to 30% tumor after enrichment and is not appropriate for assays in which identification of subclonal events (eg, resistance mutations) is important. If Sanger sequencing is utilized, tumor enrichment methodologies are nearly always recommended.
- Any method that interrogates sequences other than a subset of highly specific alterations (eg, NGS, Sanger) has the potential to identify variants of uncertain significance (VUS). Any variant classified as a VUS, even if in a gene in which other variants are clinically actionable, should not be considered as a basis for therapy selection.
- Other methodologies may be utilized, including multiplex approaches not listed above (ie, SNaPshot, MassARRAY).
- Fluorescence in situ hybridization (FISH) analysis is utilized for many assays examining copy number, amplification, and structural alterations such as gene rearrangements".

The NCCN states, "To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *ALK* rearrangements, *BRAF* mutations, *EGFR* mutations, *KRAS* mutations, *METex14* skipping mutations, *NTRK* 1/2/3 gene fusions, *RET* rearrangements, and *ROS1* rearrangements. Both FDA and laboratory-developed test platforms are available that address the need to evaluate these and other analytes. Broad molecular profiling is also recommended to identify rare driver mutations for which effective therapy may be available, such as high-level *MET* amplifications and *ERBB2* mutations".

The NCCN also states that, "First-line targeted therapy is recommended for eligible patients with metastatic NSCLC and positive test results for actionable driver mutations such as, *ALK*, *BRAF p.V600E*, *EGFR*, *METex14* skipping, *NTRK 1/2/3*, *RET*, and *ROS1.* Second-line targeted therapy is recommended for patients with metastatic NSCLC and positive test results for *EGFR exon 20* insertions or *KRAS p. G12C mutations*".

In the 2022 NCCN update, the NCCN clarified that "any variant that is classified as a VUS should not be used to select targeted therapy even if the VUS occurs in a gene in which other variants are clinically actionable".

The NCCN Panel added important information about general standards for biomarker testing in eligible patients with NSCLC. They noted that broad molecular profiling is molecular testing that "identifies all of the established actionable driver mutations described in the algorithm (eg. *ALK*, *BRAF*, *EGFR*, *KRAS*, *METex14* skipping, *NTRK 1/2/3*, *RET*, *ROS1*) – using either a single assay or a combination of a limited number of assays—and optimally also identifies the emerging actionable molecular biomarkers, including high-level *MET* amplification and *ERBB2* mutations. Tiered testing approaches, based on the low prevalence of co-occurring biomarkers, are acceptable".

EGFR mutations

EGFR mutations are most often assessed using RT-PCR, Sanger sequencing, and NGS. *EGFR* mutation status is important for determining use of tyrosine kinase inhibitor (TKI) therapies. *EGFR* mutations include, but are not limited to, exon 19 deletions, p.L858R point mutation, p.L861Q, p.G719X, p.S768I0, exon 20 insertion variants, and p.T790M. As a category 1 recommendation, *EGFR* mutation testing is recommended for advanced or metastatic disease, including adenocarcinoma, large cell, and NSCLC NOS. As a category 2A recommendation, it is recommended to consider it for individuals with squamous cell carcinoma who have never been smokers, small biopsy specimens, or mixed histology.

ALK gene rearrangements

ALK gene rearrangements are most often assessed using FISH, but IHC can also be effective. The NCCN states that NGS can detect *ALK* fusions, but PCR is less likely to detect any ALF fusion with a novel partner(s). The most common fusion partner for *ALK* is EML4; however, other partners have been isolated and identified. Like *EGFR*, *ALK* status is used in determining whether TKI therapies are appropriate. As a category 1 recommendation, *ALK* testing is recommended for advanced or metastatic disease, including adenocarcinoma, large cell, and NSCLC NOS. As a category 2A recommendation, it is recommended to consider it for individuals with squamous cell carcinoma who have never been smokers, small biopsy specimens, or mixed histology.

ROS1 rearrangements

In NSCLC, *ROS1* rearrangements can result in inappropriate *ROS1* kinase signaling. Similar to *ALK*, FISH break-apart testing is often used, but this methodology "may under-detect the FIG-*ROS1* variant". IHC requires confirmatory testing because it has a low specificity for *ROS1*. PCR, if used, can be unlikely to detect novel fusion partners. The use of NGS can detect *ROS1* fusions, but DNA-based NGS is prone to under-detection of *ROS1* fusions. *ROS1* status is important for responsiveness to oral *ROS1* TKIs. As category 2A recommendations, *ROS1* testing should be performed for advanced or metastatic disease, including adenocarcinoma, large cell, and NSCLC NOS; it should be considered in individuals with squamous cell carcinoma with small biopsy specimens or mixed histology. Entrectinib has been noted as a preferred treatment option for *ROS1* rearrangements in advanced or metastatic NSCLC by the NCCN since 2019.

BRAF point mutations

Sequencing methods, especially NGS and Sanger, and rtPCR are most often used for detecting *BRAF* point mutations. *BRAF* V600 mutations are associated with responsiveness to certain combination therapies. Many *BRAF* mutations have been identified in NSCLC, but the impact of these mutations is not well-understood as of date. As category 2A recommendations, *BRAF* testing should be performed for advanced or metastatic disease, including adenocarcinoma, large cell, and NSCLC NOS; it should be considered in individuals with squamous cell carcinoma with small biopsy specimens or mixed histology.

KRAS point mutations

Like *BRAF*, sequencing methods are used in the identification of point mutations within the *KRAS* gene. For NSCLC, the most common *KRAS* mutations are located in codon 12 even though other point mutations may occur elsewhere. *KRAS* mutations have been linked as a prognostic indicator of poor survival and can impact *EGFR* TKI therapy. The NCCN states, "*EGFR, KRAS, ROS1*, and *ALK* genetic alterations do not usually overlap; thus, testing for *KRAS* mutations may identify patients who will not benefit from further molecular testing." A newly designed oral KRAS G12C inhibitor was found to be effective in use against the *KRAS* p.G12C mutation, but this class of inhibitor has not been evaluated

for any other mutations.

MET exon 14 skipping variants

NGS-based testing, particularly RNA-based as it provides improved detection, is used to detect *METex14* skipping events. Immunohistochemistry is not used. Oral TKI therapy is used to address a *METex14* skipping mutation when detected.

RET

FISH break-apart probe methodology is one appropriate method used to detect a RET mutation, though it may under-detect some fusions. Sequencing methods such as NGS and rtPCR are effective but rtPCR has difficulty detecting fusions with novel partners. RNA-based NGS has better fusion detection capability than DNA-based NGS. Regardless of fusion partner, *RET* mutations are responsive to oral *RET* TKI therapies.

PD-L1

PD-L1 is expressed on tumor cells; its presence is used to determine possible pembrolizumab therapy. The FDA has approved IHC use for assessing PD-L1. The FDA-approved companion diagnostic for PD-L1 guides utilization of pembrolizumab in patients with NSCLC and is based on the tumor proportion score. The NCCN does note that "the potential for multiple different assays for PD-L1 has raised concern among both pathologists and oncologists." As a category 1 recommendation, PD-L1 testing is recommended for all cases of advanced or metastatic disease, including adenocarcinoma, large cell, NSCLC NOS, and squamous cell carcinoma.

NTRK gene fusion

The NCCN has an *NTRK* gene fusion positive algorithm where larotrectinib is to be used as a first-line therapy if the gene fusion was discovered prior to first-line systemic therapy. If the *NTRK* gene fusion was discovered during a different first-line systemic therapy, then they recommend completing the planned systemic therapy, including maintenance therapy, and then follow this first-line therapy up with larotrectinib. As a category 2A recommendation, the NCCN recommends *NTRK* gene fusion testing to be included as part of molecular profiling for all forms of advanced or metastatic disease, including adenocarcinoma, large cell, NSCLC NOS, and squamous cell carcinoma. "The NCCN NSCLC Panel recommends larotrectinib and entrectinib (both are category 2A) as either first-line or subsequent therapy options for patients with *NTRK* gene fusion-positive metastatic NSCLC based on data and the FDA approvals. As of the v3 2020 update, both agents are considered "preferred" first-line therapies for patients with *NTRK* gene fusion-positive metastatic disease

Tumor Mutational Burden (TMB)

"TMB is considered to be an emerging biomarker that may be useful in selecting patients for nivolumab with or without ipiliumab; however, there is no consensus on how to measure TMB." In 2019, the NCCN added tumor mutational burden (TMB) to the list of biomarkers to identify novel therapies and in the section concerning predictive biomarkers. The NCCN goes on to state, "Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications… Thus, the NCCN Panel strongly advises broader molecular profiling to identify rare driver mutations to ensure that patents receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents".

Emerging biomarkers to identify novel therapies

The NCCN version 2.2022 also lists the following emerging biomarkers to identify novel therapies for patients with metastatic NSCLC.

Genetic Alteration	**Available Targeted Agents for Genetic Alteration**
High-level *MET* amplification	Crizotinib Capmatinib Tepotinib
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine Fam-trastuzumab deruxtecan-nxki

College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology

The CAP/IASLC/AMP joint guidelines indicate that "*EGFR* molecular testing should be used to select patients for *EGFR*-targeted TKI [tyrosine kinase inhibitor] therapy" (Evidence Grade: A). 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)" (Lindeman et al, 2013). The 2018 CAP guidelines 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).

The 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 CAP 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". However, the CAP states 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" and that "[*RET, MET*, *KRAS*, 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, KRAS*, and *ERBB* (*HER2*)] as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative".

The guidelines indicate that "*ALK* molecular testing should be used to select patients for *ALK*-targeted TKI therapy" (Evidence Grade: B). 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).

The CAP recommends 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".

The 2018 CAP recommendations 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".

The 2018, CAP 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".

In 2018, CAP 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 *ALK* TKI 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".

American Society of Clinical Oncology (ASCO)

The ASCO published a joint update on "Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations" with Ontario Health (OH). These guidelines are intended for patients without alterations in *EGFR* or *ALK*. These recommendations divide PD-L1 expression into three categories: negative (0%), low positive (1-49%) and high (>50%). Pembrolizumab, carboplatin, pemetrexed, atezolizumab, paclitaxel, and bevacizumab are all listed as potential treatments, some of which may stand alone and some which are to be used in combination.

Another joint update with Cancer Care Ontario remarked that "Mutations in *KRAS* are not predictive for benefit from adjuvant chemotherapy".

ASCO published an endorsement of the joint guidelines from the CAP/IASLC/AMP with minor modifications. Relevant differences from the joint guidelines include:

- *BRAF* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
- Physicians may use molecular biomarker testing in tumors with an adenocarcinoma component or nonsquamous non–small-cell histology (in addition to "any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver (eg, young age [50 years]; light or absent tobacco exposure)".

European Society for Medical Oncology (ESMO)
According to 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. NGS is also mentioned for *ALK*, *RET*, *ROS1*, *MET, HER2*, and *BRAF* mutations.

ESMO remarks that the role of targeted agents in stages I-III NSCLC have not been evaluated properly. Therefore, they state that "there is no role for targeted agents in stage III NSCLC outside clinical trials".

ESMO published a guideline regarding metastatic NSCLC in 2020. In it, they note *EGFR, ALK, ROS1, BRAF*, and PD-L1 expression as usable biomarkers for "personalised medicine." *HER2, MET*, *NTRK*, and *RET* are considered "evolving targets/biomarkers". ESMO's specific recommendations are listed below:

- "*EGFR* mutation status should be systematically analysed in advanced NSCC [non-small cell lung cancer] [level of evidence "I", strength of recommendation "A"]. Test methodology should have

adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined"

- "The availability of TKIs effective against T790M-mutant recurrent disease makes T790M testing on disease relapse mandatory [I, A]"

- "Testing for *ALK* rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A]"

- "Testing for *ROS1* rearrangement should be systematically carried out in advanced NSCLC [III, A]. Detection of the *ROS1* translocation by FISH remains a standard; IHC may be used as a screening approach [IV, A]"

- "*BRAF* V600 mutation status should be systematically analysed in advanced NSCLC for the prescription of *BRAF*/MEK inhibitors"

- "Molecular *EGFR* and *ALK* testing are not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers"

- "If available, multiplex platforms (NGS) for molecular testing are preferable [III, A]."

- "PD-L1 IHC should be systematically determined in advanced NSCLC [I, A]"

- "Testing is required for pembrolizumab therapy but may also be informative when nivolumab or atezolizumab are used".

In 2021, EMSO published an update to previous guidelines focusing mainly on therapeutics and adjuvant treatment with targeted precision therapies.

National Institute for Health and Care Excellence (NICE)

NICE has published a guideline on the diagnosis and management of lung cancer. In it, NICE discusses treatment regimens for various tumor subtypes, such as *EGFR* positive, *ALK1* rearrangement positive, *ROS1* positive, and PD-L1 percentage. However, NICE makes these recommendations for stage IIIB cancer as well as stage IV non-squamous cancer.

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration
Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
June 01, 2023	Policy created
December 03, 2024	Policy approved by Medical Directors
December 20, 2024	Policy approved at UMC
March 01, 2025	Policy effective date following notification period