Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer

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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 results in a reclassification of lung tumors to include molecular subtypes that may direct targeted therapy or immunotherapy depending on the presence of specific variants.

Lung cancer is the leading cause of cancer death in the United States. In 2022, an estimated 236,740 new cases (117,910 in men and 118,830 in women) of lung and

bronchial cancer will be diagnosed, and 130,180 deaths (68,820 in men and 61,360 in women) are estimated to occur because of the disease. Only 19% of all patients with lung cancer are alive 5 years or more after diagnosis. However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, and advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), targeted therapies, and immunotherapies. Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 50%, depending on the biomarker.

Non-Small Cell Lung Cancer
Treatment options for non-small-cell lung cancer (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, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%. 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.

ALK Rearrangements
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. Most BRAF variants occur more frequently in smokers.

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 2 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%.

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.

KRAS variants can be detected by direct sequencing, PCR technologies, or NGS.

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.

There are currently no targeted therapies specifically approved for this indication.

MET Gene
MET alteration is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR TKIs.

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.

PD-1/PD-L1

Programmed cell ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

ROS1 Rearrangements
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%. Patients with ROS1 fusions are typically never-smokers with adenocarcinoma.

RET Rearrangements
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. RET fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.

Tumor Mutation Burden (TMB)
Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.

Targeted Treatment and Immunotherapy
Targeted treatments and immunotherapy for the variants described above are summarized in the below table:

Target	FDA-Approved Therapies
ALK	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig)

	• Lorlatinib (Lorbrena)
BRAF	• Dabrafenib and trametinib combination
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva), • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro) • Amivantamab-vmjw (Rybrenant)
HER2	• No FDA-approved targeted treatements
KRAS	• Sotorasib (Lumakras)
MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko
NTRK	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq)
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)

ROS1	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Lorlatinib (Lorbrena) • Entrectinib (Rozlytrek)

Biomarker Testing using Tissue Biopsy to Select Targeted Therapy for Advanced-Stage Non-Small Cell Lung Cancer (NSCLC)

Clinical Context and Test Purpose
The purpose of identifying targetable oncogenic "driver mutations" in patients who have non-small cell lung cancer (NSCLC) is to inform a decision whether patients should receive a targeted therapy versus another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, systemic therapy was cytotoxic chemotherapy. However, certain patients may be good candidates for treatment with targeted therapies or immunotherapy. The goal of targeted therapies is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

Populations
The relevant population of interest are individuals with advanced NSCLC who are being considered for targeted therapy.

Intervention
The intervention of interest is testing for somatic genome alterations known as "driver mutations," specifically for EGFR, BRAF, KRAS, ERBB2 (HER2) variants; ALK, ROS, RET rearrangements; MET alterations, NTRK gene fusions.

Comparator
The following practice is currently being used to target therapy for advanced-stage NSCLC: standard management without testing for driver mutations. Standard management consists primarily of chemotherapy, although some patients are candidates for immunotherapy.

Outcomes
Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved quality of life (QOL) associated with receiving a more effective and less cytotoxic targeted therapy than chemotherapy in those with driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months to 1year.

Review of Evidence
The evidence is presented below, by variant
(EGFR, ALK, BRAF, ROS1, KRAS, HER2, RET, MET, NTRK) and by recommended therapy.

ALK Gene Rearrangements
ALK gene rearrangements most often consist of an inversion in chromosome 2, which leads to fusion with the echinoderm microtubule-associated protein like 4 (*EML4*) gene and a novel fusion oncogene EML4-ALK. This inversion causes abnormal expression and activation of ALK tyrosine kinase.

ALK Rearrangement Frequency
ALK rearrangements occur in 3% to 6% of NSCLC.

FDA-Approved Companion Diagnostic Tests for ALK Rearrangements
Several methods are available to detect ALK gene rearrangements or the resulting fusion proteins in tumor specimens including FISH, immunohistochemistry, reverse transcription-PCR of cDNA, and NGS. Two tests have been approved by the FDA as companion diagnostics to detect ALK rearrangements for treatment with crizotinib: the Vysis ALK Break Apart FISH Probe Kit and Ventana ALK (D5F3) CDx Assay.

The Vysis kit is a FISH-based assay. The clinical validity of the Vysis ALK Break Apart FISH Probe Kit was demonstrated in a retrospective analysis of patients screened for a phase 2, open-label single-arm study of crizotinib in patients with stage IIIB or IV NSCLC. The response rate for crizotinib in 136 *ALK*-positive patients was 50% (95% CI, 42% to 59%) with a median duration of response of 42 weeks (range, 6 to 42 weeks). The response rate for 19 *ALK*-negative patients was 26% (95% CI, 9% to 51%).

The Ventana assay is an immunohistochemical-based assay. The clinical validity of the Ventana ALK (D5F3) CDx Assay was demonstrated in a retrospective analysis of patients screened for an open-label RCT of crizotinib versus platinum-doublet chemotherapy in patients with stage IIIB or IV NSCLC. The concordance between the Ventana and Vysis tests were calculated using patient samples analyzed at an independent, central laboratory. The PPA was 86.0% (95% CI, 80.2% to 90.4%) and the NPA was 96.3% (9%% CI, 94.7% to 97.4%). Overall, in 343 patients who were *ALK*-positive by the Vysis assay, crizotinib was associated with longer PFS compared with

chemotherapy (HR, 0.45; 95% CI, 0.36 to 0.60). In the subset of 141 patients who were also *ALK*-positive by the Ventana assay, the results were similar (HR, 0.40; 95% CI, 0.25 to 0.64). In the 25 patients who were *ALK*-positive by the Vysis assay and *ALK*-negative by the Ventana assay, the relative effect of crizotinib was not clear (HR, 1.71; 95% CI, 0.43 to 6.79).

Companion diagnostic tests have been FDA approved to select patients with NSCLC for treatment with the ALK inhibitors ceritinib, alectinib, and brigatinib, *see Regulatory Status below.*

Tyrosine Kinase Inhibitors

Crizotinib
The ccelerated approval of crizotinib by the FDA was based on phase 1 and 2 trials in which crizotinib showed marked antitumor activity in patients with *ALK*-positive advanced NSCLC, with an ORR of 60% and PFS range from 7 to 10 months. These results were confirmed in 2 subsequent phase 3 trials.

A phase 3, open-label trial randomized 347 patients with previously treated, locally advanced, or metastatic *ALK*-positive lung cancer to oral crizotinib twice daily (n=173) or chemotherapy (n=174) every 3 weeks. All patients had received 1 platinum-based chemotherapy regimen before the trial. The extent of metastatic disease was 95% and 91% in patients in the crizotinib and chemotherapy groups, respectively, and tumor histology was adenocarcinoma in 95% and 94%, respectively. The primary endpoint was PFS. Patients in the chemotherapy group who experienced progressive disease were allowed to cross over to crizotinib as part of a separate study. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; p<.001). Partial response rates with crizotinib were 65% (95% CI, 58% to 72%) and 20% (95% CI, 14% to 26%) with chemotherapy (p<.001). Interim analysis of OS showed no significant improvement with crizotinib compared with chemotherapy (HR for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; p=.54). The median follow-up for OS was 12.2 in the crizotinib group and 12.1 months in the chemotherapy group. Patients reported greater reductions in lung cancer symptoms and greater improvement in global QOL with crizotinib than with chemotherapy.

A phase 3, open-label trial compared crizotinib and chemotherapy in 343 previously untreated patients with *ALK*-positive advanced nonsquamous NSCLC. Patients were randomized to oral crizotinib twice daily or pemetrexed plus cisplatin or carboplatin every 3 weeks for up to 6 cycles. If there was disease progression for patients receiving chemotherapy, crossover to crizotinib was allowed. Progression-free survival was the primary endpoint; PFS was 10.9 months compared with 7.0 months for the groups that received crizotinib and chemotherapy, respectively (HR for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; p<.001) and ORRs (complete and partial responses) were 74% and 45%, respectively (p<.001). The median OS was not reached in

either group. The probability of 1-year survival with crizotinib was 84% and 79% with chemotherapy. Crizotinib was associated with greater patient-reported reductions in lung cancer symptoms and greater improvements in QOL.

Other ALK Inhibitors
Certinib has demonstrated superior efficacy concerning PFS when compared with chemotherapy in both the first line and second line (following crizotinib) settings in the ASCEND-4 and ASCEND-5 RCTs.

Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2, phase 2 studies. Alectinib has also shown superior efficacy and lower toxicity when compared with crizotinib in the first line setting in the ALEX and J-ALEX phase 3 RCTs.

Brigatinib has shown promise in early phase 1 and 2 studies with PFS of almost 13 months in patients with crizotinib-refractory disease. The FDA approval was granted to brigatinib in 2017 for the treatment of patients with *ALK*-positive NSCLC who have progressed on or are intolerant of crizotinib. Approval was based on an open-label, multicenter clinical trial that reported a durable overall response rate

Section Summary
Cirzotinib was granted accelerated approval by the FDA in 2011 for patients with locally advanced or metastatic NSCLC, based on ORRs observed in 2, single-arm trials. Two subsequent, phase 3 trials have shown superior PFS and tumor response rates and improved QOL in patients with crizotinib versus chemotherapy, in both previously untreated and untreated *ALK*-positive advanced NSCLC. The FDA has approved 2 companion diagnostics for detecting *ALK* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib. Companion diagnostic tests have been FDA approved to select patients with NSCLC for treatment with ALK inhibitors.

BRAF Gene Variants

FDA-Approved Companion Diagnostic Tests for BRAF Variants
BRAF variants are detected by PCR sequencing or NGS methods. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect *BRAF* V600E variants to aid in selecting NSCLC patients for treatment with combination dabrafenib (Tafinlar) and trametinib (Mekinist) therapy. The Oncomine test is an NGS oncology panel that detects, among other variants, *BRAF* V600E variants from DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. The detection of *BRAF* V600E variants by the test was evaluated by retrospective analyses of a phase 2, multicenter, nonrandomized study that included patients with a *BRAF* V600E variant who had progressed on prior treatment or were treatment-naive who were treated with dabrafenib in combination with trametinib in the study. Patients were screened for a *BRAF* V600E variant based on local lab tests used at each enrollment site. No FDA-approved test was available for detection of *BRAF* V600E variants in FFPE NSCLC

specimens, so a validated PCR assay (BRAF V600 PCR Mutation Test) was used to estimate concordance. The concordance between the Oncomine test and the BRAF V600 PCR Mutation Test was 100% for PPA (95% CI, 95% to 100%) and 100% for NPA (95% CI, 97% to 100%). The response rate in the 57 previously treated patients in the study who were *BRAF*-positive by local lab test was 67% (95% CI, 53% to 79%) compared with 73% (95% CI, 50% to 89%) for the 22 patients who were also *BRAF*-positive by Oncomine. The response rate in the 36 treatment-naive patients who were *BRAF*-positive by local lab test was 61% (95% CI, 44% to 77%) compared with 61% (95% CI, 39% to 80%) in the 23 patients who were also *BRAF*-positive by Oncomine.

In June 2017, the FDA approved an additional indication for use of dabrafenib and trametinib combination therapy in patients with NSCLC with the *BRAF* V600E variant as detected by an FDA-approved test. The Oncomine Dx Target Test was approved as a companion diagnostic.

BRAF Inhibitors

Dabrafenib and Trametinib

The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled in 3 cohorts: cohorts A and B had received at least 1 previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than 3 prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease. Trial results for cohorts A, B, and C were reported by Planchard et al (2016, 2017), cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy. In summary, the response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of whom had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at 8 weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those who were treatment naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. Squamous cell carcinomas and other dermatological side effects were reported.

Section Summary

The FDA has approved a companion diagnostic for detecting *BRAF* variants to aid in selecting NSCLC patients for treatment with combination BRAF and MEK inhibitors, dabrafenib and trametinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. The FDA expanded the indication for dabrafenib and trametinib to include the treatment of NSCLC patients whose tumors have a *BRAF* V600E variant based on a multicenter, single-arm study that included a cohort of 57 patients who had progressed on prior therapy and a cohort of 36 treatment-naive patients. Dabrafenib and trametinib combination therapy were effective in patients with a *BRAF* V600E variant, with a response rate of about 60% in both cohorts. Lower response rates were reported in other nonrandomized studies of

BRAF inhibitor monotherapy in patients who had previously progressed on prior treatments.

EGFR Gene Variants
Somatic variants in the tyrosine kinase domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858) are the most commonly found *EGFR* variants associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs; afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an EGFR TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

EGFR Variant Frequency
Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC). In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), *EGFR* variant prevalence (all exon 19 deletion or L858R) was 23.8%.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies.[10,] Eberhard et al observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al observed *EGFR* variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

In 2 other studies, the acquired *EGFR* T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.

U.S. Food and Drug Administration Approved Companion Diagnostic Tests for EGFR Variants
EGFR-sensitizing and -resistance variants can be detected by direct sequencing, polymerase chain reaction (PCR) technologies, or next-generation sequencing (NGS). Gene sequencing is considered an analytic criterion standard. A report by the Canadian Agency for Drugs and Technologies in Health, conducted by Mujoomdar et al analyzed *EGFR* variants. Based on 11 observational studies, the report authors concluded that PCR-based approaches identify *EGFR* variants with a sensitivity equivalent to that of direct sequencing.

Several tests have been approved as companion diagnostics to detect *EGFR*-resistance variants (exon 19 deletions or exon 21 L858R substitutions) for at least 1 of the EGFR TKIs (afatinib, erlotinib, gefitinib, or osimertinib): the therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, cobas EGFR Mutation Test v1 and v2, Oncomine Dx Target Test, and FoundationOne CDx. The cobas v2 test also is approved

as a companion diagnostic to detect the T790M resistance variant to select patients for treatment with osimertinib.

The clinical validity of the therascreen RGQ PCR kit was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT comparing afatinib with chemotherapy in treatment-naive patients with stage IIIB or IV NSCLC, in which the *EGFR* variants for enrollment were determined using a clinical trial assay (CTA) conducted at central laboratories. The positive percent agreement (PPA) of therascreen versus CTA for detection of *EGFR*-sensitizing variants was 98% (95% confidence interval [CI], 95% to 99%) and negative percent agreement (NPA) was 97% (95% CI, 94% to 99%). Overall, a statistically significant efficacy benefit for afatinib versus chemotherapy was reported in the *EGFR*-positive patients as measured by the therascreen EGFR RGQ PCR Kit (hazard ratio [HR], 0.49; 95% CI, 0.35 to 0.69) that was similar to the efficacy in the overall population, which was *EGFR*-positive by the CTA (HR, 0.58; 95% CI, 0.43 to 0.78).

The clinical validity of the cobas EGFR Mutation Test v1 was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT comparing erlotinib with chemotherapy in treatment-naive patients with advanced NSCLC. In this RCT, the *EGFR* variants for enrollment were determined with a CTA at a central laboratory using Sanger sequencing first for determination of *EGFR* variants status, followed by confirmatory testing for exon 19 deletions and exon 21 L858R variants=. The PPA of cobas versus CTA for detection of *EGFR*-sensitizing variants was 94% (95% CI, 89% to 97%) and NPA was 98% (95% CI, 95% to 99%). Overall, a statistically significant efficacy benefit for erlotinib versus chemotherapy was reported in the *EGFR*-positive patients as measured by the cobas EGFR Mutation Test v1 (HR, 0.34; 95% CI, 0.21 to 0.54) that was similar to the efficacy in the overall population, which was *EGFR*-positive by the CTA (HR, 0.34; 95% CI, 0.23 to 0.49). The cobas EGFR Mutation Test v2 expanded the indication for the use of the cobas EGFR Mutation Test to include the detection of the exon 20 (T790M) substitution variant in NSCLC patients for whom osimertinib (Tagrisso) treatment is indicated. The clinical validity of the cobas EGFR Mutation Test v2 was demonstrated in retrospective analyses of patients enrolled in a phase 2, single-arm study of osimertinib for *EGFR*-sensitizing variant-positive metastatic NSCLC who had progressed following prior therapy with an approved EGFR TKI. The osimertinib response rate in the patients identified as *EGFR* T790M-positive by the cobas v2 test was 62% (95% CI, 55% to 69%).

The clinical validity of the Oncomine Dx Target Test was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT, which included newly diagnosed patients with stage IIIB or IV or recurrent NSCLC, in which the *EGFR* variant for enrollment was determined using therascreen. The PPA of Oncomine versus therascreen for detection of *EGFR*-sensitizing variants was 99% (95% CI, 93% to 100%) and NPA was 99% (95% CI, 96% to 100%). No data on the effectiveness of gefitinib in patients identified as *EGFR*-positive by Oncomine were reported.

The clinical validity of FoundationOne CDx was demonstrated by assessing the concordance of the test with results from mass spectrometry, gel sizing, fluorescence in situ hybridization (FISH), and immunohistochemistry of clinical tumor tissue specimens. Test sensitivity ranged from 95% to 99% across alteration types, with a positive predictive value exceeding 99%. No data on the effectiveness of targeted therapy in patients identified as *EGFR*-positive by FoundationOne CDx were reported.

Tyrosine Kinase Inhibitors

Combined Analysis
A meta-analysis by Lee et al (2013), which evaluated 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC, reported improved progression-free survival (PFS) in *EGFR* variant-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. Comparators were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among *EGFR* variant-negative patients, PFS was improved using EGFR TKIs compared with placebo maintenance but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome.

A TEC Assessment (2007) evaluated *EGFR* variants and TKI therapy in advanced NSCLC. It concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* variant testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. An updated Assessment (2010), with revised conclusions, indicated that *EGFR* variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

Other meta-analyses have confirmed the PFS and OS results and conclusions for *EGFR*-positive patients have been published.

Erlotinib

Systematic Review
Petrelli et al eported a meta-analysis (13 randomized trials) of 1260 patients with *EGFR*-mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy. The comparator was standard therapy. Overall, reviewers noted that the use of EGFR TKIs increased the chance of obtaining an objective response almost 2-fold compared with chemotherapy. Response rates were 70% versus 33% in first-line trials and 47% versus 28.5% in second-line trials. Tyrosine kinase inhibitors reduced the hazard of progression by 70% in all trials and by 65% in first-line trials; however, they did not improve OS.

Randomized Controlled Trials
Many additional publications have provided data on *EGFR* variants in tumor samples obtained from NSCLC patients treated with erlotinib. Nine of these were nonconcurrent prospective studies of treatment-naive and previously treated patients who received erlotinib and were then tested for the presence or absence of variants. Four others were prospective, single-arm enrichment studies of variant-positive or wild-type patients treated with erlotinib. In 3 studies of *EGFR* variant-positive patients, the objective radiologic response was 40% to 70%, the median PFS was 8 to 14 months, and the median OS was 16 to 29 months. In patients with wild-type tumors, the objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.

Gefitinib

Systematic Reviews
A Cochrane review by Sim et al (2018) compared the use of gefitinib with no therapy or chemotherapy as first-line, second-line, or maintenance therapy for NSCLC. The literature search was conducted in February 2017 and identified 35 RCTs (N=12,089 patients) for inclusion. For the general population of patients with NSCLC, gefitinib did not improve OS when given as first- or second-line therapy but did improve PFS when administered as maintenance therapy. In the subset of patients with *EGFR* variants, gefitinib improved PFS compared with first- and second-line chemotherapy and improved both OS and PFS when administered as maintenance therapy.

Randomized Controlled Trials
Three randomized controlled trials (RCTs) included 668 patients with stage IIIB or IV NSCLC and *EGFR*-sensitizing variants. All reported clinically and statistically significant improvement in PFS (HR range, 0.30 to 0.49) but no improvement in OS with gefitinib compared with chemotherapy. Grade 3 or greater adverse events occurred in fewer patients in the gefitinib groups. The Iressa Pan-Asia Study (IPASS) trial enrolled patients with and without *EGFR*-sensitizing variants. The investigators reported a significant interaction between treatment and *EGFR* variant status for PFS (interaction p<.001); PFS was longer for gefitinib in patients with *EGFR*-sensitizing variants and shorter for gefitinib in patients without *EGFR*-sensitizing variants. Another 3-arm RCT in Tables 4 and 5 compared a combination of chemotherapy plus gefitinib with chemotherapy alone and gefitinib alone.[43,] Patients in the combined treatment arm experienced longer OS compared with chemotherapy and gefitinib alone.

Wu et al (2017) conducted a post hoc subgroup analysis focusing on Asian patients in the IPASS trial who were randomized to gefitinib (n=88) or carboplatin/paclitaxel (n=98). The analysis found that patients with the *EGFR* variant who received gefitinib experienced longer PFS than patients receiving chemotherapy (HR, 0.5; 95% CI, 0.4 to 0.8).

Afatinib

Unlike erlotinib and gefitinib, which selectively inhibit EGFR, afatinib inhibits not only EGFR but also human epidermal growth factor receptor 2 (HER2) and HER4 and may have activity in patients with acquired resistance to TKIs. Such patients often harbor a T790M variant (substitution of threonine by methionine at codon 790) in *EGFR* exon 20. The efficacy and safety of afatinib were evaluated in the LUX-Lung series of studies.

LUX-Lung 3 was an RCT including 345 patients with stage IIIB or IV, *EGFR* variant-positive, lung adenocarcinoma who were previously untreated for advanced disease. Seventy-two percent of patients were Asian, 26% were white, and 90% (308 patients) had common *EGFR* variants (exon 19 deletion or L858R substitution variant in exon 21). Patients received afatinib or chemotherapy (cisplatin plus pemetrexed). In a stratified analysis of patients with common *EGFR* variants, the median PFS was 13.6 months for the afatinib group and 6.9 months for the chemotherapy group (HR, 0.47; 95% CI, 0.34 to 0.65; p=.001). The median PFS for the 10% of patients who had other *EGFR* variants was not reported, but the median PFS for the entire patient sample was 11.1 months in the afatinib group and 6.9 months in the chemotherapy group (HR, 0.58; 95% CI, 0.43 to 0.78; p=.001). The incidence of objective response in the entire patient sample was 56% in the afatinib group and 23% in the chemotherapy group (p=.001). With a median follow-up of 16.4 months, the median OS was not reached in any group; preliminary analysis indicated no difference in OS between the 2 treatment groups in the entire patient sample (HR, 1.12; 95% CI, 0.73 to 1.73; p=.60). Patients in the afatinib group reported greater improvements in dyspnea, cough, and global health status/QOL than those in the chemotherapy group. Grade 3 or higher diarrhea, rash, and paronychia (nail infection) occurred in 14%, 16%, and 11% of afatinib-treated patients, respectively, and in no patients in the chemotherapy group. Grade 3 or higher mucositis (primarily stomatitis) occurred in 9% of the afatinib group and 1% of the chemotherapy group.[48,] Similar results were reported by Wu et al (2014) in a phase 3 trial conducted in 364 Asian patients (Lux-Lung 6), which compared afatinib with gemcitabine plus cisplatin.[50,] Progression-free survival was 11.0 in the afatinib group and 5.6 months in the chemotherapy group (HR, 0.28; 95% CI, 0.20 to 0.39) and the response rates were 67% and 23%, respectively.

Three other published LUX-Lung studies evaluated patients with stage IIIB or IV lung adenocarcinoma who were previously treated for advanced disease, but design features limit interpretation of results.

- LUX-Lung 2 was a single-arm study (2012) of afatinib in 129 patients (87% Asian, 12% white) with *EGFR* variant-positive disease. Patients had been treated with chemotherapy but not with *EGFR*-targeted therapy; approximately half of the patients (enrolled after a protocol amendment) were chemotherapy-naive. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common *EGFR* variants (exon 19 deletion or L858R) and in 39% of 23 patients with other *EGFR* variants. The median PFS was 13.7 months in patients with common *EGFR* variants and 3.7 months in patients with other *EGFR* variants (p not reported). Results for variant-negative patients were not reported.

- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous treatment with erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 (66% Asian, 33% white) of 585 enrolled patients were *EGFR* variant-positive (76 common *EGFR* variant-positive) In this group, the median PFS was 3.3 months in the afatinib group and 1.0 month in the placebo group (HR, 0.51; 95% CI, 0.31 to 0.85; p=.009). In 45 variant-negative patients, the median PFS was 2.8 months in the afatinib group and 1.8 months in the placebo group, a statistically nonsignificant difference (p=.22), possibly due to small group sizes. LUX-Lung 4 was a single-arm study (2013) of afatinib in 62 Japanese patients. Objective responses occurred in 2 (5%) of 36 patients with common *EGFR* variants and in none of 8 patients with other *EGFR* variants (p>.05).

Osimertinib

In 2015, the U.S. Food and Drug Administration (FDA) granted accelerated approval to osimertinib for treatment of metastatic *EGFR* T790M variant-positive NSCLC patients who have progressed on or after EGFR TKI therapy. The therapy was approved with an FDA-approved companion test, the cobas EGFR Mutation Test v2, which is a blood-based genetic test to detect *EGFR* variants including the T790M variant. Approval was based on 2 multicenter, single-arm studies.

The osimertinib label describes the 2 studies. Eligible patients had metastatic *EGFR* T790M variant-positive NSCLC and had progressed on prior systemic therapy, including an EGFR TKI. Patients received osimertinib 80 mg once daily. The first study enrolled 201 patients: the second enrolled 210 patients. The major efficacy outcome measure of both trials was the objective response rate (ORR) assessed by a blinded, independent review committee. The median duration of follow-up was 4.2 months in the first study and 4.0 months in the second. The ORR was similar in the 2 studies. The pooled ORR was 59% (95% CI, 54% to 64%); 0.5% achieved a complete response and 59% achieved a partial response. The most common adverse reactions were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. Fatal adverse reactions included the following: 4 patients with interstitial lung disease/pneumonitis; 4 patients with pneumonia, and 2 patients with cerebral vascular accident/cerebral hemorrhage.

One randomized controlled trial (RCT) has compared osimertinib with chemotherapy. Osimertinib was associated with clinically and statistically significantly prolonged PFS and higher response rates than chemotherapy and had lower rates of grade 3 and 4 adverse events. However, interstitial lung disease-like adverse events and QT prolongation were more common with osimertinib. Another RCT compared osimertinib with other EGFR TKIs (gefitinib or erlotinib) as first-line therapy.[56,] The results suggested a reduced risk for central nervous system progression with osimertinib compared with other TKIs.

Comparative Effectiveness of EGFR TKIs

As the previous sections have shown, erlotinib, gefitinib, afatinib, and osimertinib all have improved efficacy compared with chemotherapy in patients who have NSCLC and *EGFR*-sensitizing variants and are well tolerated. Randomized controlled trials, as well as systematic reviews and meta-analyses of the RCTs, directly comparing the EGFR TKIs with each other and with chemotherapy, have been conducted.

Systematic Reviews

The systematic reviews and meta-analyses included overlapping trials. Randomized controlled trials included in the reviews and analyses differed in study design, treatments compared, and line of treatment (first-, second-, or third-line). In general, patients who are EGFR-positive and treated with TKIs experienced longer PFS than patients treated with chemotherapy. Meta-analyses comparing different TKIs reported inconsistent results, with some analyses finding various TKIs comparable and other analyses finding some TKIs more effective than others. Safety data were not consistently available among the RCTs, limiting adverse event comparisons among treatments.

Randomized Controlled Trials

Soria et. al. (2018) conducted a double-blind phase 3 trial comparing osimertinib with other TKIs (gefitinib or erlotinib) for the first-line treatment of patients with *EGFR*-positive advanced NSCLC. Median PFS was longer with osimertinib (18.9 months; 95% CI, 15.2 to 21.4 months) than with the other TKIs (10.2 months, 95% CI, 9.6 to 11.1 months; HR, 0.5, 95% CI, 0.4 to 0.6). Objective response rate did not differ significantly between osimertinib and the other TKIs. Follow-up was not long enough to adequately determine OS.

Two RCTs compared gefitinib with erlotinib in patients who had *EGFR*-sensitizing variants. Urata et al (2016) reported on a phase 3 RCT of 401 patients with *EGFR* variants randomized to gefitinib or erlotinib. The median PFS was 8.3 months (95% CI, 7.2 to 9.7 months) for patients receiving gefitinib and 10.0 months (95% CI, 8.5 to 11.2 months) for those receiving erlotinib. Rash was more common with erlotinib (18.1% vs. 2.2%) while both alanine aminotransferase elevation and aspartate aminotransferase elevation were more common with gefitinib (6.1% vs 2.2% and 13.0% vs. 3.3%, respectively). Similarly, Yang et al (2017) reported a median PFS of 13.0 months for erlotinib and 10.4 months for gefitinib (HR, 0.81; 95% CI, 0.62 to 1.05) in 256 patients, with no differences in rates of grade 3 or 4 adverse events.

LUX-7 was a phase 2b, head-to-head trial of afatinib versus gefitinib for the treatment of first-line *EGFR* variant-positive (del19 and *L858R*) adenocarcinoma of the lung.[68,] LUX-7 randomized 319 patients in a 1:1 ratio to afatinib 40 mg/d or gefitinib 250 mg/d, stratified by variant type (del19 and L858R) and brain metastases (present vs. absent). In the overall population, PFS was significantly improved with afatinib than with gefitinib (HR, 0.73; 95% CI, 0.57 to 0.95; p=.02). Time-to-treatment failure also showed improvement in favor of afatinib (HR, 0.73; 95% CI, 0.58 to 0.92; p=.01). The ORR was significantly higher in the afatinib group (70% vs. 56%; p=.01). Several grade 3 or 4

adverse events were more common with afatinib than with gefitinib including diarrhea (13% vs. 1%) and rash (9% vs. 3%); liver enzyme elevations were more common with gefitinib (0% vs. 9%). Serious events occurred in 11% of patients in the afatinib group and 4% in the gefitinib group.

Section Summary
Several randomized controlled trials (RCTs), nonconcurrent prospective studies, single-arm enrichment studies, and meta-analyses of RCTs have demonstrated that patients with *EGFR*-sensitivity variants benefit from erlotinib, gefitinib, or afatinib therapy and patients with *EGFR*-resistance variant (T790M) benefit from osimertinib. Patient populations in these studies primarily had adenocarcinoma. Currently, there is little evidence to indicate that *EGFR* variant testing can guide treatment selection in patients with squamous cell histology. The FDA has approved several companion diagnostics for detecting *EGFR* variants to aid in selecting NSCLC patients for treatment with erlotinib, gefitinib, afatinib, and osimertinib.

Patients who are found to have wild-type tumors are unlikely to respond to erlotinib, gefitinib, or afatinib. These patients should be considered candidates for alternative therapies.

KRAS Gene Variants

FDA-Approved Companion Diagnostic Tests for KRAS Variants
KRAS variants can be detected by direct sequencing, PCR technologies, or NGS.

In 2021, FDA approved Therascreen KRAS RGQ PCR kit and Guardant360 CDx as companion diagnostic tests to select patients for treatment with the KRAS inhibitor, sotorasib.

There are no FDA approved companion diagnostic tests for detecting KRAS variants to select patients for treatment with EGFR TKI therapy.

RAS Inhibitor
Skoulidis et al (2021) reported results of a phase 2, open-label trial of sotorasib in patients with KRAS variant NSCLC (Tables 14 and 15). Presence of the KRAS alteration in tissue was confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% CI: 6.9 to not evaluable).

Tyrosine Kinase Inhibitors
Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analyses of phase 3 trials of TKIs in patients with wild-type (nonmutated) versus *KRAS*-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and meta-analyses.

Systematic Reviews

Pooled data on the relation between *KRAS* variants and response to EGFR TKI therapy are insufficient to determine an association between *KRAS* variant status and treatment effects on PFS or OS.

Pan et al (2016) published a meta-analysis of 41 studies (N = 13,103 patients) of prognostic and predictive values of a *KRAS* variant in NSCLC. Having a *KRAS* variant was significantly associated with poorer OS (HR, 1.6; 95% CI, 1.4 to 1.8) and disease-free survival (HR, 1.57; 95% CI, 1.2 to 2.1) in early-stage resected NSCLC, and with inferior outcomes of EGFR TKI treatment (relative risk, 0.21; 95% CI, 0.1 to 0.4) in advanced NSCLC. Having a *KRAS* variant was still significantly associated with poorer OS (HR, 1.4; 95 % CI, 1.2 to 1.6) and PFS (HR, 1.4; 95 % CI, 1.1 to 1.6) of EGFR TKIs when patients with *EGFR* variants were excluded.

Mao et al performed a meta-analysis of 22 studies in 1470 patients with NSCLC (1335 [91%] evaluable for response), 231 (17%) of whom had *KRAS* variants. Studies were heterogeneous in-patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary endpoint was ORR, defined as the sum of complete and partial response. Objective response rates for patients with *KRAS* and wild-type *KRAS* variants were 3% and 26%, respectively. Incomplete reporting of survival data precluded meaningful assessment of the effect of *KRAS* status on survival in NSCLC patients treated with EGFR TKIs. Data for PFS and OS stratified by *KRAS* status were available in 8 studies. The median PFS in *KRAS*-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. The median OS in *KRAS*-mutated and wild-type patients was 4.7 and 10.7 months, respectively. However, only 2 studies presented HRs with 95% CIs for PFS and OS and, therefore, a pooled analysis to derive an overall HR was not performed.

Linardou et al (2008) performed a meta-analysis of 17 studies with 1008 patients, 165 (16.4%) of whom had a *KRAS* variant. Eligible studies reported response (complete or partial) stratified by *KRAS* variant status. Primary endpoints were sensitivity and specificity of *KRAS* testing, defined as *KRAS* variant carriers showing no response to erlotinib (stable disease or progressive disease) and *KRAS* wild-type patients showing a response, respectively. Sensitivity and specificity were assessed overall and in subgroups defined by TKI received (gefitinib and/or erlotinib), response criteria (Response Evaluation Criteria in Solid Tumors [RECIST] or World Health Organization), possible selection bias, and previous chemotherapy, if any. There was no significant difference in sensitivity or specificity across subgroups. The presence of a *KRAS* variant was associated with a lack of response to TKIs (sensitivity, 21%; 95% CI, 16% to 28%; specificity, 94%; 95% CI, 89% to 97%; positive likelihood ratio, 3.52; negative likelihood ratio, 0.84). (For the analysis, likelihood ratios were calculated using pooled estimates for sensitivity and specificity.) Reviewers concluded that *KRAS* variants conferred a high level of resistance to anti-EGFR therapies; however, this conclusion was tentative due to limitations of selected studies (e.g., lack of individual patient data, heterogeneity of response endpoints, treatment regimens, patient selection criteria,

retrospective design of included studies). Furthermore, incomplete reporting of survival data precluded meaningful assessment of the effect of the *KRAS* variant on survival.

Retrospective Reviews

Papadimitrakopoulou et al (2016) reported on the results of the A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer (BATTLE-2) phase 2 study. The BATTLE-2 program is an umbrella study evaluating the effects of targeted therapies focusing on *KRAS*-mutated cancers. Two hundred patients with advanced NSCLC tumors who did not have *EGFR* variants or *ALK* gene fusions whose cancer was refractory to more than 1 prior therapy were assigned to 1 of 4 arms using adaptive randomization: erlotinib (n=22), erlotinib plus MK-2206 (n=42), MK-2206 plus AZD6244 (n=75), or sorafenib (n=61), stratified by *KRAS* status. AZD6244 and MK2206 are targeted small-molecule drugs that inhibit MEK and AKT, respectively. Sorafenib is a multitargeted signal transduction inhibitor that inhibits raf-kinases, vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor-B, and c-kit. Only 186 evaluable patients were included in analyses. The 8-week disease control rate was 20%, 25%, 62%, and 44% for the 4 treatment groups, respectively, in the *KRAS* variant-positive patients. For *KRAS* wild-type patients, disease control rate was 36%, 57%, 49%, and 47%, respectively. The median PFS did not differ by *KRAS* status.

Rulli et al (2015) reported on results from biomarker analyses in the Tarceva Italian Lung Optimization tRial (TAILOR) trial.[96,] TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for *KRAS* and *EGFR* variant status. Wild-type *EGFR* patients (n=218) received first-line platinum-based chemotherapy and then were randomized at progression to erlotinib or docetaxel. *KRAS* variants were present in 23% of randomized patients. The presence of a *KRAS* variant was not associated with PFS (HR, 1.01; 95% CI, 0.71 to 1.41; p=.98) or OS (HR, 1.24; 95% CI, 0.87 to 1.77; p=.23). The treatment effect did not differ by *KRAS* status (test for interaction: OS p=.97; PFS p=.42)

Observational Studies

Fiala et al (2013) retrospectively analyzed patients with NSCLC who underwent *EGFR*, *KRAS*, and *PIK3CA* (phosphatidylinositide-3-kinase catalytic subunit-alpha) variant testing. Of 215 patients tested, 16 (7.4%) had a *KRAS* variant. Of 174 tested patients treated with an EGFR TKI (erlotinib or gefitinib), median PFS in 14 *KRAS*-mutated patients was 1.3 months versus 2.0 months in *KRAS* wild-type patients (n=160 [92%]); the difference was not statistically significant (p=.120). Median OS in this treated group was 5.7 months in *KRAS*-mutated patients and 8.2 months in *KRAS* wild-type patients, a statistically significant difference (p=.039). The authors concluded that *KRAS* variant status might have a negative prognostic role, but a predictive role was not confirmed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution in China. Patients with *KRAS* variants were randomized by the tumor, node, metastasis stage, time of the first visit within 1 year, and histology, to

both *EGFR* variant-positive and *KRAS/EGFR* wild-type patients. Seventy (4%) patients received EGFR TKI therapy. In this group, median PFS was 11.8 months and 2.0 months in patients with *EGFR* and *KRAS* variants, respectively, and 1.9 months in wild-type patients. Compared with wild-type patients, PFS was statistically longer in patients with *EGFR* variants (p<.001) but no different in patients with *KRAS* variants (p=.48). The authors observed that "the presence of an *EGFR* variant, but not a *KRAS* variant, was predictive of responsiveness to EGFR TKI treatment."

Anti-EGFR Monoclonal Antibodies

Two, phase 3 trials (BMS099, FLEX) investigated platinum-based chemotherapy with and without cetuximab in the first line setting for advanced NSCLC. Subsequently, investigations of *KRAS* variant status and cetuximab treatment were performed for both trials.

In the multicenter, phase 3 BMS099 trial, 676 chemotherapy-naive patients with stage IIIB or IV NSCLC were assigned to taxane and carboplatin with or without cetuximab. The primary endpoint was PFS; secondary endpoints were overall response rate, OS, QOL, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. The trend in OS favoring cetuximab was not statistically significant. A post hoc correlative analysis was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab.[104,] Of the original 676 enrolled patients, 202 (29.9%) had tumor samples available for *KRAS* testing. *KRAS* variants were present in 35 (17%) patients. Among patients with wild-type *KRAS*, OS was similar for the cetuximab-containing arm (n=85) and the chemotherapy-alone arm (n=82) (HR, 0.93; 95% CI, 0.67 to 1.30; p=.68; median survival, 9.7 months, and 9.9 months, respectively). Among patients with *KRAS* variants, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy-alone arm (n=22) (HR, 0.91; 95% CI, 0.45 to 2.07; p=.93; median survival, 16.8 months and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions for the presence of *KRAS* variants and outcomes evaluated; treatment differences favoring the addition of cetuximab in the *KRAS*-mutated subgroup were consistent with those observed in the wild-type *KRAS* subgroup and in the overall study population. The authors concluded that the results did not support an association between *KRAS* variant status and lack of cetuximab benefit. However, the results should be interpreted with caution due to small subgroup sample sizes and the retrospective nature of the analysis.

In the open-label, randomized, phase 3 FLEX trial, 1125 chemotherapy-naive patients with stage III or IV, NSCLC were randomized to chemotherapy plus cetuximab (n=557) or chemotherapy alone (n=568). The primary endpoint was OS. Patients who received chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs. 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; p=.04). Subsequently, *KRAS* variant testing was performed on archived tumor tissue of 395 (35%) of 1125 patients. *KRAS* variants were detected in 75 (19%) tumors. Among patients with mutated *KRAS*, the median OS in the cetuximab-containing

(n=38) and chemotherapy-alone arms (n=37) was similar (8.9 months vs. 11.1 months, respectively; HR, 1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type *KRAS*, the median OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (11.4 months vs. 10.3 months, respectively; HR, 0.96; 95% CI, 0.75 to 1.23; p=.74). Progression-free survival also was similar in the cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR, 0.97; 95% CI, 0.76 to 1.24) and wild-type (HR, 0.84; 95% CI, 0.50 to 1.40) *KRAS*. Response rates in the cetuximab-containing arm in patients with *KRAS*-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=.96). Overall, there was no indication that *KRAS* variant status was predictive of cetuximab effect in NSCLC.

MEK Inhibitors

Two randomized controlled trials (RCTs) have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with *KRAS*-positive advanced NSCLC after progression with first-line therapy. MEK inhibitor therapy did not improve PFS compared with docetaxel alone; response rates were similar or marginally improved. Grade 3 or higher adverse events were more frequent with MEK inhibitor therapy compared with docetaxel.

Section Summary

In a phase 2 trial of sotorasib conducted in 126 patients with KRAS variant NSCLC confirmed with the use of the Therascreen KRAS RGQ PCR Kit, overall response was 37.1% (95% CI 28.6% to 46.2%) with an acceptable safety profile. In an analysis of secondary endpoints, PFS was 6.8 months (95% CI 5.1 to 8.2) and OS was 12.5 months (95% CI 10.0 to not evaluable).

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although 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 *KRAS* testing beyond *EGFR* testing.

A lack of response to EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is largely restricted to patients with wild-type *KRAS*. The expectation that *KRAS* variant status also would be an important predictive marker for cetuximab response in NSCLC has not been shown. In 2 randomized trials with post hoc analyses of *KRAS* variant status and use of 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.

Two randomized controlled trials (RCTs) have compared a MEK inhibitor with docetaxel in patients with *KRAS*-positive advanced NSCLC who had progression following first-line therapy. The MEK inhibitor did not improve PFS compared with docetaxel; the

response rate was marginally improved. Grade 3 or higher adverse events were more frequent with the MEK inhibitors.

HER2 Gene Variants

Mok et al (2016) reported on the biomarker subgroup analyses from the FASTACT-2 study. FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study of intercalated first line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIB or IV NSCLC. In addition to analyzing for *EGFR*, *HER2* and *HER3* biomarkers were analyzed by immunohistochemistry. Only *EGFR* variants (p<.001) were predictive of outcomes; *HER2 and HER3* biomarkers were not significant.

Shen et al (2015) retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for *HER2* expression. *HER2* overexpression was detected in 24 patients. The ORRs in patients with and without *HER2* overexpression were 29% and 14%, respectively (p=.12). The median PFS and OS in patients with and without *HER2* overexpression did not differ statistically significantly (PFS, 4.7 months vs. 3.9 months, p=.09; OS, 21 months vs. 19 months, p=.09).

Mazières et al (2013) reported on a retrospective review of a consecutive series of patients with NSCLC tested for a *HER2* variant and assessed clinicopathologic characteristics and patient outcomes by variant status. A *HER2* variant was identified in 65 (1.7%) of 3800 patients and was mutually exclusive of other driver mutations (*EGFR*, *ALK*, *BRAF*), except for a case in which both a *HER2* and a *KRAS* variant were identified. The patient population in which a *HER2* variant was found had a median age of 60 years (range, 31 to 86 years), 69% were women, and 52% were never-smokers. All tumors were adenocarcinomas, and 50% were stage IV (n=33). Patients with stage IV disease received conventional chemotherapy and, of these, 16 patients also received *HER2*-targeted therapy as additional lines of therapy (for a total of 22 evaluable individual anti-*HER2* treatments). Four patients had progressive disease, 7 had disease stabilization, and 11 with partial response. Progression-free survival for patients with *HER2* therapies was 5.1 months.

Section Summary

Studies of *HER2* variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions.

MET Gene Variants

FDA-Appproved Companion Diagnostic Tests for MET Gene Variants

Foundation One CDx and FoundationOne Liquid CDx are FDA approved as companion diagnostics for capmatinib for the treatment of NSCLC harboring MET with an exon 14 skipping alteration.

Capmatinib
In 2020, FDA approved the MET inhibitor capmatinib for treatment of adult patients with metastatic NSCLC whose tumors have an alteration that leads to MET exon 14 skipping. Approval was accelerated based on overall response rate and duration of response in the GEOMETRY mono-1 trial (NCT02414139).

Section Summary
The GEOMETRY Mono-1 trial showed efficacy of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation, especially in treatment-naive patients (68% [95% CI, 48% to 84%]) and median duration of 12.6 months). Efficacy was also observed in pre-treated patients (overall response rate 41% [95% CI 29% to 53%] and median duration of 9.7 months).

NTRK Gene Fusions

FDA-Approved Companion Diagnostic Tests for NTKR Gene Fusions
There are currently no FDA-approved companion diagnostic tests for NTRK gene fusions.

Larotrectinib
Drilon et al (2018) evaluated the effectiveness of larotrectinib in 55 patients with consecutively and prospectively identified tropomyosin receptor kinase (TRK) fusion-positive solid tumors, including 4 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 FDA approved larotrectinib for patients with TRK fusion-positive solid tumors based on these results. An updated analysis of 153 patients from this data set was consistent with the earlier analysis.

Entrectinib
Doebele et. al. (2020) published an analysis of 3 phase 1-2 trials of entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumors. Of 54 patients, 10 (19%) had NSCLC. AT a median follow-up of 12.9 months, 31 of 54 patients had an objective response (57%; 95% CI 43.2 to 70.8). Median duration of response was 10 months (95% CI 7.1 to not estimable). The most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (7 [10%] of 68 patients in the NTRK fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anemia (8 [12%] and 16 [5%]). The most common serious treatment-related adverse events were nervous system disorders (3 [4%] of 68 patients and 10 [3%] of 355 patients). No treatment-related deaths occurred.

Section Summary
From studies of 55 patients with consecutively and prospectively identified *NTRK* fusion-positive solid tumors, including 4 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. In an integrated analysis of 3 phase 1-2 trials in patients with NTRK solid tumors, 10 of whom had NSCLC, response was 57% (95% CI 43.2% to 70.8%) with an acceptable safety profile.

RET Gene Variants

FDA-Approved Companion Diagnostic Tests for RET Gene Variants
Oncomine DxTarget is FDA approved as a companion diagnostic for pralsetinib for the treatment of metastatic RET fusion-positive NSCLC.

Kinase Inhibitors
In May 2020, FDA granted accelerated approval for selpercatinib for the treatment of adult patients with metastatic RET fusion-positive NSCLC. Approval was based on the overall response observed in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO) in patients whose tumors had RET alterations. There is currently no FDA-approved companion diagnostic test for selpercatinib.

In September 2020, FDA approved pralsetinib for treatment of metastatic RET-fusion positive NSCLC along with the Oncomine Dx Target Test companion diagnostic. This indication was approved under the FDA's Accelerated Approval program, based on data from the phase I/II ARROW study. The ARROW study is an ongoing and not yet published in a peer review journal, but trial results are available in the FDA multi-discipline review of praseltinib. The FDA reviewers noted that for NSCLC, overall response rates may be considered an endpoint reasonably likely to predict clinical benefit when the treatment effect size is large, and the responses are durable.

Section Summary
The FDA has approved a companion diagnostic (Oncomine Dx Target Test) for treating metastatic *RET*-fusion positive NSCLC with pralsetinib under accelerated approval based on studies of effect particularly among treatment naive patients (70% [95% CI, 50% to 86%]). The FDA has also approved selpercatinib for the treatment of adult patients with metastatic *RET* fusion-positive NSCLC based on a multicenter, open-label, multicohort clinical trial in patients whose tumors had *RET* alterations, with high treatment naive effect (85% [95% CI, 70% to 94%]).

ROS1 Gene Rearrangements

FDA-Approved Companion Diagnostic Tests for ROS1 Rearrangements
Several methods are available to detect *ROS1* translocations including FISH, immunohistochemistry, quantitative real-time reverse transcription-PCR, and some NGS panels. FISH is considered the standard method. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The Oncomine test is an NGS oncology panel that detects, among other variants, fusions in *ROS1* from RNA

isolated from FFPE tumor tissue samples. The clinical validity of the detection of *ROS1* rearrangements by the test was evaluated by a retrospective analysis of FFPE NSCLC specimens obtained from patients enrolled in a *ROS1* cohort from an ongoing single-arm, phase 1 safety study of crizotinib in patients with advanced cancer. *ROS1* fusion status was determined by a validated FISH comparator test for the study. Concordance between the Oncomine Dx Target Test and the FISH test as well as clinical outcomes were reported in the Summary of Safety and Effectiveness Data. A total of 157 specimens were included. The PPA for Oncomine versus FISH was 80% (95% CI, 59 to 93) and NPA was 100% (95% CI, 97% to 100%). For all *ROS1*-positive patients, as originally detected for enrollment into the *ROS1* cohort, the response rate was 72% (95% CI, 58% to 84%). For *ROS1*-positive patients as detected by Oncomine, the response rate was 83% (95% CI, 36% to 99.6%).

Tyrosine Kinase Inhibitors

Crizotinib

In 2016, after an expedited review, the FDA expanded the indication for crizotinib to include the treatment of patients whose metastatic NSCLC tumors have a *ROS1* rearrangement. The approval was based on a 2014 multicenter, single-arm study that enrolled 50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement. The study assessed an expansion cohort of the phase 1 PROFILE 1001 Trial. Patients were given oral crizotinib (250 mg twice daily) in continuous 28-day cycles; the median duration of treatment was 65 weeks. A companion *ROS1* biomarker diagnostic test was not approved at the time of the crizotinib indication expansion. However, the Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori).

In summary, a nonrandomized trial and an observational study of crizotinib have shown response rates of greater than 70% in patients with *ROS*1 rearrangements, the majority of whom had progressed on prior therapy.

Ceritnib

One nonrandomized trial of ceritinib reported response rates of about 60%. Adverse events were similar to those seen in patients with *ALK* rearrangements using ALK TKIs. Common low-grade side effects included gastrointestinal side effects, visual impairment, and pain. Grade 3 or higher adverse events included liver function abnormalities and pneumonia.

Kim et al (2013) reported on clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to *ROS1*-rearrangement status. *ALK* rearrangements and *EGFR* variants were concurrently analyzed. The patients had clinical stages ranging from I to IV, but most were stage IV (41.3%). Of the 208 tumors, 3.4% (n=7) were *ROS1* rearranged. *ROS1* rearrangement was mutually exclusive from *ALK* rearrangement, but 1 of 7 *ROS1*-positive patients had a

concurrent *EGFR* variant. Patients with *ROS1* rearrangement had a higher ORR and longer median PFS on pemetrexed than those without a rearrangement. In patients with *ROS1* rearrangement, PFS with EGFR TKIs was shorter than those patients without the rearrangement. None of the *ROS1*-positive patients received ALK inhibitors (e.g., crizotinib), which is the recommended targeted therapy for patients with NSCLC and this genetic alteration.

Entrectinib
Drilon et al 2020 onducted an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib. At median followup of 15.5 months (interquartile range 13.4 to 20.2), 41 of 53 patients had an objective response (77%; 95% CI 64% to 88%), with a median duration of response of 24.6 months (95% CI 11.4 to 34.8). In the safety-evaluable population 46 (34%) of 134 patients had grade 3 or 4 treatment-related adverse events. There were no treatment-related deaths. There is currently no FDA-approved companion diagnostic test for entrectinib.

Section Summary
The FDA has approved a companion diagnostic for detecting *ROS1* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. The FDA expanded the indication for crizotinib to include the treatment of patients whose tumors have a *ROS1* rearrangement based on a multicenter, single-arm study including 50 patients, the majority of whom had progressed on prior therapy. Crizotinib was effective in patients with *ROS1* rearrangements, with a response rate of about 70%. Similar response rates were reported in other nonrandomized studies of crizotinib and ceritinib. In an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the ORR was 77%, with a median duration of response of 24.6 months. There is currently no FDA-approved companion diagnostic test for entrectinib.

Immonotherapy for Advanced Non-Small cell Lung cancer

Clinical Context and Test Purpose
The purpose of identifying PD-L1 expression and tumor mutational burden (TMB) in patients who have advanced NSCLC is to inform a decision whether patients should receive a immunotherapy versus another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, systemic therapy was cytotoxic chemotherapy. Targeted treatments are ineffective in patients whose tumors lack genetic alterations such as EGFR, ALK, BRAF, and ROS1 variants (driver mutations). However, a subset of these patients may be good candidates for treatment with immunotherapy. The goal of immunotherapy is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

Populations
The relevant population of interest is individuals with advanced NSCLC who are being considered for immunotherapy.

Interventions
The interventions of interest are testing for PD-L1 and TMB.

Compartors
Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective and less cytotoxic targeted therapy than chemotherapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those whose tumors do not express PD-L1.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those whose tumors express PD-L1; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective immunotherapy and delay in initiation of chemotherapy in those whose tumors do not express PD-L1.

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months and 1 year.

Review of Evidence

PD-L1 Testing

FDA Companion Diagnostics Tests for PD-L1
Companion diagnostic tests have been FDA-approved for PD-L1 testing for immunotherapy with atezolizumab, pembrolizumab, and the combination of nivolumab plus ipilimumab in patients with NSCLC.

Atezolizumab
Herbst et. al. (2020) published results of a phase 3, open label RCT of atezolizumab compared to platinum-based chemotherapy in 572 patients with NSCLC who had not previously received chemotherapy and who had PD-L1 expression on at least 1% of tumor cells or at least 1% of tumor-infiltrating immune cells (NCT02409342).[118,] In the subgroup of patients with tumors who had the highest expression of PD-L1 (205 patients), the median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; HR for death, 0.59; p=.01). Atezolizumab treatment resulted in significantly longer OS than platinum-based chemotherapy among patients with NSCLC with high PD-L1 expression, regardless of histologic type. Grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the atezolizumab group and the chemotherapy group, respectively.

Pembrolizumab
Reck et.al. (2016) published results of the KEYNOTE-024 Trial (NCT02142738), which compared pembrolizumab to platinum-based chemotherapy in 305 patients with NSCLC and PD-L1 expression on at least 50% of tumor cells.[119,] At a median follow-up of 11.2 months, PFS was longer with pembrolizumab compared with chemotherapy (median PFS, 10.3 vs. 6 months; HR, 0.50; 95% CI, 0.37 to 0.68). The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group.

Nivolumab in Combination with Ipilimumab
In the CHECKMATE 227 Trial (NCT02477826) reported by Hellmann et al (2019), among the patients with a PD-L1 expression level of 1% or more, the median duration of OS was 17.1 months (95% CI, 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (p=.007), with 2-year OS rates of 40.0% and 32.8%, respectively. The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Section Summary
In randomized controlled trials (RCTs) individuals with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Tumor Mutational Burden Testing to Select Patients for Immunotherapy

FDA-Approved Companion Diagnostic Testing
There is no FDA approved companion diagnostic test for tumor mutational burden (TMB) to select patients for treatment with nivolumab plus ipilimumab. FoundationOne CDx is FDA approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors.

Randomized Controlled Trials
In a subgroup analysis of the CHECKMATE 227 trial (NCT02477826), PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB (≥10 mutations per megabase).

In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS, and OS in patients receiving immunotherapy.

Pembrolizumab

Nonrandomized Trial
Marabelle et. al. (2020) reported the association of high TMB with response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study. High TMB was defined as >10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-high group and was 33.1 months in the non-TMB-high group. Notably, TMB-high status was associated with improved response irrespective of PD-L1. Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors (ie, PD-L1 combined positive score of ≥1) and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors.

Section Summary
In a subgroup analysis of an RCT, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB (≥10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. In a prespecified subgroup analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors. In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies.

Biomarker Testing using Circulating Tumor DNA (Liquid Biopsy) to Select Targeted Therapy or Immunotherapy for Advanced-Stage Non-Small Cell Lung Cancer

Selecting Targeted Therapy

Clinical Context and Test Purpose
The purpose of identifying targetable oncogenic "driver mutations" such as *EGFR* variants in patients who have NSCLC is to inform a decision whether patients should receive a targeted therapy versus another systemic therapy. Patients have traditionally been tested for driver mutations using samples from tissue biopsies.

One testing strategy is to use liquid biopsy to select first line and second-line treatments in patients with advanced NSCLC, with reflex to tissue biopsy if the test is negative. This testing strategy is based on the reflex testing strategy suggested in the U.S. Food and Drug Administration (FDA) approval for the cobas test. Some guidelines have suggested

a different testing strategy wherein testing with a liquid biopsy is considered only when testing with a tissue biopsy is not feasible.

Populations
The target population consists of patients with NSCLC where tumor biomarker testing is indicated to select a treatment. Patients may be treatment-naive or being considered for a treatment change due to progression, recurrence, or suspected treatment resistance.

Treatment recommendations for patients with advanced NSCLC are usually made in the tertiary care setting ideally in consultation with a multidisciplinary team of pathologists, thoracic surgeons, and oncologists.

Routine surveillance or periodic monitoring of treatment response as potential uses of the liquid biopsy were not evaluated in this evidence review.

Interventions
The technology considered is an analysis of tumor biomarkers in peripheral blood (liquid biopsy) to determine treatment selection. Several commercial tests are available and many more are in development. In contrast to tissue biopsy, guidelines do not exist establishing the recommended performance characteristics of liquid biopsy.

- Circulogene's Liquid Biopsy Test
- ClearID Biomarker Expression Assays
- ClearID Lung Cancer
- ctDX Lung
- FoundationOne Liquid CDx
- GeneStrat
- Guardant360
- Guardant360 CDx
- Guardant360 Tissue Next
- InVision
- LiquidGX
- OncoBeam
- Oncomine DX Target Test Lung
- PlasmaSelect 64
- Resolution ctDx Lung Assay
- Signatera Lung
- Target Selector
- Tempus xF Liquid Biopsy Pane

The evidence is considered separately for the different biomarkers. Studies have evaluated liquid biopsy for biomarkers that detect *EGFR* TKI sensitization, concentrating on the *EGFR* exon 19 deletion and *EGFR* L858R variants. Studies have also evaluated separately biomarkers associated with TKI resistance, concentrating on the *EGFR* T790M variant.

Studies have also assessed a liquid biopsy for detection of the *EML4-ALK* fusion oncogene and its variants, translocation between *ROS1* and other genes (most commonly *CD74*), *BRAF* variants occurring at the V600 position of exon 15, and other variants.

Comparators
The relevant comparator of interest is testing for variants using tissue biopsy.

Outcomes
The outcomes of interest are OS and cancer-related survival. In the absence of direct evidence, the health outcomes of interest are observed indirectly as a consequence of the interventions taken based on the test results.

In patients who can undergo tissue biopsy, given that negative liquid biopsy results are reflexed to tissue biopsy, a negative liquid biopsy test (true or false) does not change outcomes compared with tissue biopsy.

Similarly, in patients who cannot undergo tissue biopsy, a negative liquid biopsy test (true or false) should result in the patient receiving the same treatment as he/she would have with no liquid biopsy test, so a negative liquid biopsy test does not change outcomes.

The implications of positive liquid biopsy test results are described below.

Potential Beneficial Outcomes with Positive Result
For patients who can undergo tissue biopsy, the beneficial outcomes of a true-positive liquid biopsy result are the avoidance of tissue biopsy and its associated complications. In the National Lung Screening Trial, which enrolled 53454 persons at high- risk for lung cancer at 33 U.S. medical centers, the percentage of patients having at least 1 complication following a diagnostic needle biopsy was approximately 11%.

For patients who cannot undergo tissue biopsy, the beneficial outcomes of a true-positive liquid biopsy result are receipt of a matched targeted therapy instead of chemotherapy and/or immunotherapy.

Potential Harmful Outcomes with Positive Results
The harmful outcome of a false-positive liquid biopsy result is incorrect treatment with a targeted therapy instead of immunotherapy and/or chemotherapy. In a meta-analysis of randomized controlled trials (RCTs) of EGFR TKIs vs chemotherapy in patients without *EGFR*-sensitizing variants, the overall median progression-free survival (PFS) was 6.4 months in patients assigned to chemotherapy vs 1.9 months in patients assigned to EGFR TKIs (hazard ratio [HR], 1.41; 95% confidence interval [CI], 1.10 to 1.81). The advantage of chemotherapy over EGFR TKIs for patients without *EGFR*-sensitizing variants was true in both the first- and second-line settings.

In the AZD9291 First Time In Patients Ascending Dose Study (AURA 1), single-arm, phase 1 trial of osimertinib, among 61 patients with *EGFR*-sensitizing variants who had progressed on an EGFR TKI but who did not have the *EGFR* T790M resistance variant, the response rate was 21% (95% CI, 12% to 34%) and median PFS was 2.8 months (95% CI, 2.1 to 4.3 months).[126,] There was no concurrent control group in AURA 1 for comparison of osimertinib with other second-line treatments among T790M-negative patients. However, in the IMpower 150 trial, the addition of the immunotherapy atezolizumab to the combination chemotherapy of bevacizumab, carboplatin, and paclitaxel improved PFS in a subset of 111 patients with *EGFR*-sensitizing variants or *ALK* translocations who had progressed on a prior targeted agent (median PFS, 9.7 months vs 6.1 months; HR=0.59; 95% CI 0.37 to 0.94).

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 6 months and 1 year.

Review of Evidence – Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
A systematic review, including 55 studies reporting clinically validity of liquid biopsy compared with tissue biopsy for detection of *EGFR* TKI-sensitivity variants or resistance variants through February 2017. Details of that systematic review are found in Appendix 1. In brief, most studies were conducted in Asia, using tests not currently being marketed in the U.S. There was high variability in performance characteristics, with sensitivities ranging from close to 0% to 98% and specificities ranging from 71% to 100%. Therefore, evidence will not be pooled across tests going forward and instead reviewed separately for tests marketed in the U.S.A systematic review by Wu et al (2015) noted sensitivity might be lower in studies including non-Asian ethnicities (55%; 95% CI, 33% to 77%) compared with Asian ethnicities (68%; 95% CI, 57% to 79%), although the difference was not statistically significant. Therefore, studies in the U.S. or similar populations will be most informative regarding the clinical validity of tests marketed in the U.S.

As previously described, there are multiple commercially available liquid biopsy tests that detect *EGFR* and other variants using a variety of detection methods. Given the breadth of molecular diagnostic methodologies available and the lack of guidelines regarding the recommended performance characteristics of liquid biopsy, the clinical validity of each commercially available test must be established independently. The market is changing rapidly, and all available tests may not be represented in the appraisal below.

Several clinical validity studies comparing liquid biopsy with tissue biopsy in patients who had advanced NSCLC for marketed tests have been published. Most have included testing for *EGFR* variants but a few included testings for less prevalent variants as well.

Evidence for the different variants is reviewed separately. Performance characteristics for detecting 1 type of variant (e.g., point mutations) may not represent performance to detect other types of variants (e.g., gene fusions).

The results of clinical validation studies of liquid biopsy compared with tissue biopsy as a reference standard, with the exception of FoundationOne Liquid CDx, which was compared to cobas EGFR Mutation Test v2 in a non-inferiority study. Although tissue biopsy is not a perfect reference standard, the terms sensitivity and specificity will be used to describe the PPA and NPA, respectively. For detection of *EGFR*-sensitizing variants, the cobas test has multiple clinical validation studies of sufficient quality and the performance characteristics are well characterized with generally high specificity (>96%). For the detection of *EGFR*-resistance variants, fewer studies are available and estimates of specificity are more variable. For the detection of less prevalent driver mutations, such as *ALK* and *ROS1* translocations, *BRAF*V600E, RET fusions, and MET exon 14 skipping, few publications are available and, in these publications, very few variants have been identified.

The cobas test has at least 6 studies (n>1500), Guardant360 CDx has at least 5 studies (n> 800), OncoBEAM has at least 3 studies (n>200), and InVision has at least 2 studies (n>400), with the majority being of adequate quality to demonstrate the performance characteristics relative to a tissue test with tight precision estimates for *specificity* for *EGFR* TKI-sensitizing variants. The FoundationOne Liquid CDx test has 1 trial (n=177) reporting non-inferiority to the cobas test; however, direct comparisons to tissue-based testing were not conducted. Other tests have promising preliminary results but none of the remaining available tests other than the cobas, Guardant360 CDx, OncoBEAM, and InVision tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for *EGFR* TKI-sensitizing variants.

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	EGFR Exon 19 deletions and EGFR Exon 21 L858R substitution	IRESSA® (gefitinib) TAGRISSO® (osimertinib) TARCEVA® (erlotinib)

Clinical validity of FoundationOne Liquid CDx assay was established as a companion diagnostic to identify patients with advanced NSCLC who may be eligible for treatment with Tarceva (erlotinib), Iressa (gefitinib), or Tagrisso (osimertinib). Two hundred and eighty retrospective samples from NSCLC patients were included in this study, which were tested for EGFR exon 19 deletion and exon 21 L858R alterations (EGFR alterations) by the FoundationOne Liquid CDx assay and the previously approved cobas® EGFR Mutation Test v2 (Roche Molecular Systems, referred to cobas assay). Both EGFR alteration-positive and EGFR alteration-negative samples (based on CTA results) were selected from the screen failed population of an unrelated clinical trial in NSCLC. To avoid selection bias, the samples were selected starting with a specific

testing date until the predefined number of 150 EGFR alteration-positive and 100 EGFR alteration-negative samples were fulfilled. Samples were tested across two replicates by the cobas assay (denoted as CCD1 and CCD2) and one replicate by FoundationOne Liquid CDx. The tested samples, from NSCLC patients, were compared against the intended use (IU) population with respect to gender to ensure the screening population is representative of the IU population. The variant cells were evaluated based on the agreement between both the FoundationOne Liquid CDx and the cobas assay results and between the two cobas assay replicates. For any samples in which there was insufficient plasma to process both CCD1 and CCD2, processing was not performed. In total there were 177 samples with complete test results available for analysis.

Agreement Analysis Results for EGFR exon 19 deletion and L858R separately

Exon 19 Deletion
PPAC1 95.5% NPAC1F 95.6% F
PPAC1 97.7% NPAC1C2 98.9% C2
PPAC2 95.5% NPAC2F 96.0% F
PPAC2 96.2% NPAC2C1 99.4% C1

L858R
PPAC1 100.0% NPAC1F 95.6% F
PPAC1 92.9% NPAC1C2 98.9% C2
PPAC2 100.0% NPAC2F 94.7% F
PPAC2 96.0% NPAC2C1 98.0 C1

Concordance Among CCD1, CCD2 and FoundationOne Liquid CDx Results with Eligible Samples (n=177)

	CCD1+			**CCD1-**		
	CCD2+	**CCD2-**	**Total**	**CCD2+**	**CCD2-**	**Total**
FoundationOne Liquid CDx+	80	4	84	1	3	4
FoundationOne Liquid CDx-	2	0	2	0	87	87
Total	82	4	86	1	90	91

Agreement Analysis Results Between FoundationOne Liquid CDx and cobas Assay

	PPA	NPA	
CCD2/CCD1*	95.3%	98.9%	
CCD1/CCD2**	96.1%	98.7%	
FoundationOne Liquid CDx/CDD1*	97.7%	95.6%	
FoundationOne Liquid DCx/CCD2**	97.7%	95.4%	

*CCD1: The 1st replicate of cobas assay as the reference
**CCD2: The 2nd replicate of cobas assay as the reference

The estimates of PPA1, PPA2, NPA1 and PA2 and the corresponding one-sided 95% upper bounds confidence limit computed using the bootstrap method are presented in the below table

	Point Estimate	Mean one-sided 95% upper confidence limit
PPA1	-2.3%	2.3%
NPA1	3.3%	6.6%
PPA2	-1.6%	4.7%
NPA2	3.3%	6.6%

Based on these results, FoundationOne Liquid CDx has been demonstrated to be noninferior to the cobas assay for the detection of EGFR exon 19 deletions and EGFR exon 21 L858R mutations in metastsic non-small cell lung cancer (NSCLC) patients. This study establishes the clinical validity of the FoundationOne Liquid CDx assay for identifying patients eligible for treatment with erlotinib, gefitinib, and osimertinib.

Section Summary
The cobas test has very high accuracy (area under the receiver operating characteristic curve, 0.96), a sensitivity above 60%, and a specificity above 96% for detection of *EGFR* TKI-sensitizing variants using tissue biopsy as the reference standard. These estimates are consistent across several studies performed using the test. The studies were performed in Asia, Europe, Australia, and the U.S., primarily in patients with advanced disease of adenocarcinoma histology. The Guardant360 CDx test has 5 studies using tissue biopsy as the reference standard performed in the U.S. in the intended-use population for *EGFR* TKI-sensitizing variants. Estimates of specificity are consistently 96% or higher. Likewise, the OncoBEAM test has 3 studies using tissue biopsy in Asia, Europe, Australia, and the U.S. in the intended-use population, 2 of which provide precise estimates for specificity that are very high (>96%). The InVision test has 2 studies using tissue biopsy as the reference standard in the U.S. and France in the intended-use population, both provide precise estimates for specificity (>96%).

For tests other than the cobas test, Guardant360 CDx, OncoBEAM, and InVision for detecting *EGFR* TKI-sensitizing variants, few studies were identified that evaluated the clinical validity of these commercially available tests for *EGFR* variants in NSCLC.

A single non-inferiority trial of FoundationOne Liquid CDx compared to the plasma-based cobas EGFR Mutation Test v2 was identified. Based on these results, FoundationOne Liquid CDx has been demonstrated to be noninferior to the cobas assay for the detection of EGFR exon 19 deletions and EGFR exon 21 L858R mutations in metastsic non-small cell lung cancer (NSCLC) patients. This study establishes the clinical validity of the FoundationOne Liquid CDx assay for identifying patients eligible for treatment with erlotinib, gefitinib, and osimertinib.

For tests of other, less prevalent, variants, such as *ALK* translocations, *ROS1* translocations, *RET fu*sions, *MET* exon 14 skipping, and *BRAF* V600E variants, few studies were identified that evaluated the clinical validity of any commercially available tests, and in these studies, very few variants were detected; therefore, performance characteristics are not well-characterized.

Few studies have examined the performance of liquid biopsy for the detection of T790M variants associated with *EGFR* TKI resistance and several different tests were used in the studies. Detection of these variants is potentially important for liquid biopsy because this variant is of interest after the initiation of treatment, when biopsies may be more difficult to obtain. Unlike the high specificities compared with tissue biopsy demonstrated for *EGFR* variants associated with TKI sensitivity, the moderate specificity means that liquid biopsy often detects T790M variants when they are not detected in tissue biopsy. Sacher et al (2016) suggested that these false positives might represent tumor heterogeneity in the setting of treatment resistance, such that the T790M status of the biopsied site might not represent all tumors in the patient.

Review of Evidence-Clinically Useful
No randomized controlled trials (RCTs) comparing management with and without liquid biopsy were identified.

Evidence on the ability of liquid biopsy to predict treatment response similar to, or better than, a tissue biopsy is also of interest. If the 2 tests are highly correlated, they are likely to stratify treatment response similarly overall. To understand the implications of "false-positive" and "false-negative" liquid biopsies for outcomes, patients who have discordant results on liquid biopsy and standard biopsy are of particular interest. If patients who are negative for *EGFR*-sensitizing or -resistance variants on liquid biopsies but positive for those variants on standard biopsies respond to EGFR TKIs (i.e., erlotinib, gefitinib, afatinib, osimertinib), it would suggest that the standard biopsy was correct and the liquid biopsy results were truly false-negatives. If patients with positive liquid biopsies and negative tissue biopsies for *EGFR* variants respond to EGFR TKIs, it would suggest that the positive liquid biopsies were correct rather than false positives.

The clinical utility might alternatively be established based on a chain of evidence. Assuming that tissue biomarkers are the standard by which treatment decisions are made, an agreement between liquid and tissue biopsies would infer that treatment selection based on liquid or tissue biopsies is likely to yield similar outcomes. Also, a liquid biopsy

would reduce the number of patients undergoing tissue sampling and any accompanying morbidity.

Depending on the analytic method, compared with a tissue biopsy, liquid biopsy appears somewhat less sensitive with generally high specificity in detecting an *EGFR* TKI-sensitizing variant that can predict outcomes. This finding suggests that an *EGFR* TKI-sensitizing variant identified by liquid biopsy could be used to select a treatment with reflex to tissue biopsy. However, evidence directly demonstrating the predictive ability of liquid biopsy would be most convincing. Also, outcomes in patients who have discordant results on liquid and tissue biopsy are of particular interest.

Therefore, BCBSA also considered evidence on the ability of liquid biopsy to predict treatment response. Liquid biopsy could improve patient outcomes if it predicts treatment response similar to, or better than, tissue biopsy. Treatment response as measured by OS outcomes would be most informative. PFS can be difficult to interpret because of confounding influences in retrospective observational subgroup analyses. Response rate may be more informative than PFS.

Some studies were nested in nonrandomized designs or RCTs. This structure potentially permits comparing associations between liquid biopsy and tissue biopsy results with outcomes. Because it has already been demonstrated by the prior studies that liquid biopsy and tissue biopsy are moderately correlated, they should both be associated with either prognosis of disease or prediction of treatment response as has been demonstrated for tissue biopsy. However, if liquid biopsy results are more strongly associated with outcomes, it might be considered better than tissue biopsy (considered the reference standard). Although liquid biopsy had a high specificity for *EGFR*-sensitizing variants (>90%) in almost all studies, false-positives could be a concern in patient populations with a low prevalence of treatable variants. Known variability of tumor tissue sampling raises concern whether false-positive liquid biopsies represent cases in which the tissue biopsy is falsely negative.

Sufficient numbers of patients have not been studied in which all possible combinations of liquid biopsy and tissue biopsy results have been analyzed for associations with patient outcomes.

The SSED document supporting the approval of Guardant360 CDx reported clinical outcome data derived from the FLAURA study, a randomized phase 3 trial of osimertinib versus gefitinib or erlotinib in the first-line treatment of patients with locally advanced and metastatic NSCLC. Patients with *EGFR* variants detected from tissue biopsies were enrolled (N=556). A subset of pretreatment plasma samples was tested with an earlier test version, Guardant360 LDT, as part of an exploratory analysis of patients who had experienced disease progression or drug discontinuation (n=189). Pre-treatment plasma samples were only available for 252/556 patients (45%) who were not previously tested with Guardant360 LDT. To mitigate selection bias, results from both CDx and LDT tests were combined and reported as Guardant360 outcomes (n=441). An *EGFR*-sensitizing

mutation was present in 304 and absent in 110 patients. Samples from 27 patients failed testing. The observed PFS for the Guardant360 population (HR, 0.41; 95% CI, 0.31 to 0.54) was similar to that observed in full FLAURA dataset (HR, 0.46; 95% CI, 0.37 to 0.57). Investigators utilized models to impute missing randomized data and consider the potential effect of Guardant360 CDx versus LDT discordance; these imputed results did not significantly deviate from the original observations (HR, 0.40 to 0.42). The SSED document also provided a concordance analysis between Guardant360 CDx and Guardant360 LDT test versions in NSCLC patients for *EGFR* exon 19 deletions, L858R, and T790M variants. Sensitivities were 96.7%, 98.1%, and 95.6%, respectively. Specificities were 98.1%, 97.2%, and 95.2%, respectively.

In Guo et al (2019), median PFS in the subset of newly diagnosed patients treated with EGFR TKIs (n=122) was compared for groups of patients with biomarker status determined by tissue biopsy and liquid biopsy. Patients with *EGFR* mutations in either tissue or liquid had a significantly improved PFS (13 months, n=68) compared to patients harboring wild-type *EGFR* in both tissue and liquid (5.4 months, n=49, p<.001). Two of 5 patients with tissue negative and liquid positive *EGFR* mutation status exhibited a PFS of 8 and 14 months, respectively. Overall PFS for this subset of patients was not reported.

The SSED document supporting the approval of the cobas EGFR Mutation Test v2 reported clinical outcome data derived from a randomized phase 3 trial of erlotinib versus gemcitabine plus cisplatin as first-line treatment of NSCLC. However, only patients with *EGFR* variants detected from tissue biopsies were enrolled. In the overall study, erlotinib showed substantial improvement in PFS over chemotherapy (HR, 0.33; 95% CI, 0.23 to 0.47), consistent with the known efficacy of erlotinib in patients with a sensitizing *EGFR* variant. Among the subset of patients with positive liquid biopsy results (77% [137/179]), erlotinib showed a similar improvement in PFS (HR, 0.29; 95% CI, 0.19 to 0.45). However, the finding has limited meaning because all patients had positive tissue biopsies, thus showing a similar result. Those with negative liquid biopsies (n=42) also showed a similar magnitude of benefit of erlotinib (HR, 0.37; 95% CI, 0.15 to 0.90), which would be consistent with liquid biopsies being false negatives.

In Zhang et al (2017), PFS in the subset of patients treated with *EGFR* TKIs (114/215) was compared for groups of patients with biomarker status determined by tissue biopsy and by liquid biopsy. The patients were primarily treated with gefitinib (n=94); 18 patients received erlotinib, 1 received icotinib, and 1 received afatinib. When patients were stratified by tissue biopsy *EGFR* status, PFS for *EGFR*-positive subjects was 342 days versus 60 days for *EGFR*-negative subjects (p<.001). Among the tissue biopsy-positive patients, there was no difference in PFS between those with positive (334 days) and negative liquid biopsies (420 days), consistent with the liquid biopsies being false-negatives. Three patients were tissue biopsy-negative, but liquid biopsy-positive; they had PFS with TKI treatment of 133, 410, and 1153 days, respectively. Although the numbers are small, the PFS values are consistent with a response to TKIs and might represent tissue biopsies that did not reflect the correct *EGFR* status.

For *EGFR*-resistance variants, Thress et al (2015) examined the response to the experimental therapeutic AZD9291 (osimertinib) by T790M status, determined using a tissue or liquid biopsy (see Table 31). Patients were not selected for treatment based on T790M status, and there was only moderate concordance between tissue and liquid biopsies. Response rates by tissue biopsy variant identification (61% for positive variants vs 29% for negative variants) were qualitatively similar to the response rates by liquid biopsy variant identification (59% for positive variants vs 35% for negative variants). Formal statistical testing was not presented. However, the authors did report response rates for patients who had positive liquid biopsies but negative tissue biopsies. In these 8 patients, the pooled response rate was 38%. The number of patients is too small to make definitive conclusions but the response rate in these patients is closer to those for patients with negative variants than with positive variants. A source of additional uncertainty in these data is that the therapeutic responses to this experimental agent have not yet been well characterized.

Oxnard et al (2016) compared outcomes by T790M status for liquid biopsy and tissue biopsy in patients enrolled in the escalation and expansion cohorts of the phase 1 AURA study of osimertinib for advanced *EGFR*-variant NSCLC. Some patients may have overlapped with the Thress et al (2015) study. Among patients with T790M-negative ctDNA, objective response rate (ORR) was higher in 45 patients with T790M-positive tissue (69%; 95% CI, 53% to 82%) than in 40 patients with T790M-negative tissue (25%; 95% CI, 13% to 41%; p=0.001), as was median PFS (16.5 months vs 2.8 months; p=0.001), which is consistent with false-negative ctDNA results. Among patients with T790M-positive ctDNA, ORR and median PFS were higher in 108 patients with T790M-positive tissue (ORR=64%; 95% CI, 54% to 73%; PFS=9.3 months) than in 18 patients with T790M-negative tissue (ORR=28%; 95% CI, 10% to 53%; p=0.004; PFS=4.2 months; p=0.0002) which is consistent with false-positive ctDNA results. The authors concluded that a T790M-variant ctDNA assay could be used for osimertinib treatment decisions in patients with acquired *EGFR* TKI resistance and would permit avoiding tissue biopsy for patients with T790M-positive ctDNA results.

Karlovich et al (2016) compared outcomes by T790M status for liquid biopsy and tissue biopsy in patients enrolled in the TIGER-X phase 1/2 clinical trial of rociletinib and an observational study in patients with advanced NSCLC. Rociletinib was an EGFR inhibitor in development for the treatment of patients with *EGFR* T790M-mutated NSCLC but the application for regulatory approval was withdrawn in 2016. The ORR was provided by cross-categories of results of tissue and ctDNA testing (see Table 31). Although CIs overlapped substantially and sample sizes in the cross-categories were small, the ORR was quantitatively largest in patients positive for T790M in both tissue and ctDNA and smaller in patients who were T790M negative in tissue regardless of ctDNA positivity.

Helman et al (2018) compared outcomes in patients with positive T790M status for liquid biopsy and tissue biopsy in patients enrolled in the TIGER-X and TIGER-2 trials of rociletinib. The ORR and PFS were provided for patients who were tissue positive and

for patients who were liquid positive (see Table 31). Both ORR and PFS were similar for the 77 patients who were identified as positive for T790M by tissue biopsy and the 63 patients identified as positive by ctDNA. Thus, 63 of 77 patients (81.8%) who had been identified as positive by tissue biopsy were also identified as positive by liquid biopsy, and this did not affect outcomes for treatment with rociletinib. As noted above, the application for regulatory approval of rociletinib was withdrawn, limiting interpretation of the effect of rociletinib.

Papadimitrakopoulou et al (2020) compared outcomes in tissue-positive T790M patients enrolled in the AURA3 (A Phase III, Open Label, Randomized Study of AZD9291 Versus Platinum-Based Doublet Chemotherapy for Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Whose Disease Has Progressed With Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Whose Tumours Harbour a T790M Mutation Within the Epidermal Growth Factor Receptor Gene) phase 3 trial of osimertinib vs platinum-pemetrexed chemotherapy after progression on *EGFR* TKI therapy. ORR and PFS HR was reported by mutation status as determined by both cobas and Guardant360 plasma tests compared to tissue as reference (see Table 31). PFS was prolonged in randomized patients (tissue T790M-positive) with a T790M-negative cobas plasma result in comparison with those with a T790M-positive plasma result in both osimertinib (median, 12.5 vs 8.3 months) and platinum-pemetrexed groups (median, 5.6 vs 4.2 months); similar outcomes were observed with Guardant360. The Guardant360 test demonstrated a significantly greater sensitivity for detection of the T790M variant compared to the cobas test ([66%, 95%CI, 59% to 72%] vs [51%, 95% CI, 44% to 58%]). Overall, patients with tissue-positive NSCLC and liquid-negative T790M status were associated with longer PFS, which may be attributable to a lower disease burden. Plasma T790M detection was associated with larger median baseline tumor size and the presence of extrathoracic disease. This observation is consistent with other studies that have observed improved plasma test sensitivity in patients with advanced stage disease and in treatment-naive patients. However, overall response rates (ORR) did not significantly differ between liquid-positive and liquid-negative groups in osimertinib-treated patients.

Merker et al (2018) reported a joint review on circulating tumor DNA for the American Society of Clinical Oncology and College of American Pathologists. The review was not specific to lung cancer but did make the following statements regarding the clinical utility of ctDNA testing for lung cancer:

- "At present, 1 PCR-based ctDNA assay for the detection of EGFR variants in patients with NSCLC has received regulatory approval in the United States and Europe, and PCR-based ctDNA assays for EGFR in NSCLC and KRAS in colorectal cancer are available for commercial use in Europe. These assays have demonstrated clinical validity, but the clinical utility in this setting is based on retrospective analyses."
- "Evidence demonstrated that, although positive EGFR testing results may effectively be used to guide therapy, undetected results should be confirmed with analysis of a tissue sample, if possible. Cases in which the variant is not detected in

the ctDNA but is detected in the tissue sample are relatively common, so undetected ctDNA assay results should be confirmed in tumor tissue testing."
- "The challenges of demonstrating clinical utility are illustrated in NSCLC. A major potential issue is that the patient population selected for study inclusion may not be representative of those targeted for the intended clinical use of the ctDNA assay."

A chain of evidence, based on the sensitivity and specificity of liquid biopsy for the detection of *EGFR* TKI-sensitizing variants such as exon deletion 19 and L858R variants, for a test that has established clinical validity (e.g., the cobas, Guardant360 CDx, OncoBEAM, or InVision tests), can support its utility for the purpose of selecting treatment with *EGFR* TKIs (e.g., erlotinib, gefitinib, afatinib, osimertinib). A robust body of evidence has demonstrated moderate sensitivity (>63%) with high specificities (>95%) for these 4 tests. If a liquid biopsy is used to detect *EGFR* TKI-sensitizing variants with referral (reflex) testing of tissue samples in those with negative liquid biopsies, then the sensitivity of the testing strategy will be equivalent to tissue biopsy, and the specificity will remain between 95% and 100%. Tissue testing of biomarkers would be avoided in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. This strategy including tissue testing will be variably efficient depending on the prevalence of detected *EGFR* variants. For example, in U.S. populations with an assumed prevalence of *EGFR* TKI-sensitizing variants of 15% and a 75% sensitive and 97% specific liquid biopsy test (e.g., cobas), 86% of the patients would then require tissue testing to detect the remaining patients with variants; 3% would receive targeted therapy after liquid biopsy who would have received a different systemic therapy if tested with tissue biopsy; and 11% would appropriately receive targeted therapy following liquid biopsy without having to undergo tissue biopsy. In other populations such as Asians where the prevalence of *EGFR* TKI-sensitizing variants is 30% to 50%, the strategy would be more efficient, and a lower proportion of patients would be subject to repeat testing. There is extremely limited evidence on whether the "false-positives" (ie, patients with positive liquid biopsy and negative tissue biopsy) might have been incorrectly identified as negative on tissue biopsy. In 1 study, 3 patients with negative tissue biopsies and positive liquid biopsies appeared to respond to *EGFR* TKI inhibitors.

The diagnostic characteristics of liquid biopsy for the detection of T790M variants associated with *EGFR* TKI-inhibitor resistance, an indication for treatment with osimertinib, has shown that liquid biopsy is moderately sensitive and moderately specific and thus overall concordance is moderate. Using tissue testing of negative liquid biopsies would increase sensitivity, but because liquid biopsy is not highly specific, it would result in false positives. Because not enough data are available to determine whether these false-positives represent a faulty tissue reference standard or are correctly labeled as false-positives, outcomes for these patients are uncertain. In 1 study, 8 patients with negative tissue biopsies but positive liquid biopsies had low response rates consistent with those with negative tissue biopsies; and in the AURA study, 18 patients with liquid-positive, tissue-negative results had a low response rate, also consistent with negative tissue biopsy. In the TIGER-X study, 3 patients who were liquid-positive, tissue-negative had low response rates to rociletinib, similar to the other tissue-negative patients.

However, although there is higher discordance in the liquid vs tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. In the AURA3 trial, T790M tissue-positive patients treated with osimertinib who were liquid-negative had longer median PFS compared to liquid-positive patients, a trend that may be associated with increased plasma test sensitivity in individuals with advanced disease.

Testing for ALK Rearrangements using FoundationOne Liquid

FDA-Approved Companion Diagnostic Test
In 2021, FDA approved FoundationOne Liquid as a companion diagnostic to detect *ALK* rearrangements to select patients for treatment with alectinib. Tissue-based tests have previously been FDA approved for this indication and as companion diagnostics for other *ALK* inhibitors.

The evidence for the clinical validity of FoundationOne Liquid to detect ALK rearrangements in patients with NSCLC was assessed in an exploratory retrospective analysis of data from the ALEX trial, described in the FDA Summary of Safety and Effectiveness Data (SSED). The analysis compared results of tissue testing using the Ventana ALK IHC assay to results from Foundation ACT, a precursor of FoundationOne Liquid. Since all patients in the bridging study were ALK positive, only PPA could be calculated. The FDA summary notes that the poor agreement between the tissue and liquid tests (PPA 69.7%; 95% CI 58.1% to 79.8%) supports the reflex recommendations for plasma negative samples to an FDA-approved tissue test.

The SSED also provides concordance data for FoundationOne Liquid compared to the clinical trial assay (CTA) from the Blood First Assay Screening Trial (BFAST) (discussed below). However, since the CTA used in BFAST was a liquid test and there was no comparison to tissue biopsy, its relevance to the assessment of clinical validity of FoundationOne liquid is limited.

The clinical utility of FoundationOne Liquid to select patients for targeted treatment with alectinib was assessed in BFAST, an ongoing, open-label Phase 2 trial of the association between blood-based NGS of genetic alterations and activity of targeted treatments in patients with advanced or metastatic NSCLC. Dziadziuszko et al (2021) reported data from the ALK-positive cohort from the study. Of 2119 patients screened, 119 (5.4%) had ALK-positive disease and 87 of these were enrolled and received alectinib (73.1%).

Section Summary
The clinical validity of FoundationOne liquid was assessed in 1 exploratory retrospective analysis of data from a randomized controlled trial (RCT) comparing crizotinib to alectinib, and in 1 clinical bridging study that compared FoundationOne Liquid to another liquid biopsy test. One nonrandomized trial directly assessed the clinical utility of FoundationOne Liquid to select patients for treatment with alectinib,

Testing for MET Exon 14 Skipping Alterations using FoundationOne Liquid

FDA-Approved Companion Diagnostic Tests

In 2021, FDA approved FoundationOne Liquid as a companion diagnostic to detect Exon 14 skipping alterations to select patients for treatment with capmatinib. A tissue-based test (FoundationOne) was previously approved as a companion diagnostic for this indication. A chain of evidence demonstrates that testing strategy with FoundationOne CDx should produce outcomes similar to tissue testing. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity.

The clinical validity of FoundationOne Liquid to detect MET Exon 14 skipping alterations in patients with NSCLC was assessed in a clinical bridging study using pre-treatment plasma samples and clinical outcome data from patients with NSCLC enrolled in the GEOMETRY mono-1 trial, an open-label, single arm, Phase 2 trial of targeted treatment with capmatinib. The clinical bridging study is described in the SSED associated with FDA approval of FoundationOne Liquid as a companion diagnostic test for capmatinib. The SSED notes that based on the low PPA between F1LCDx and the tissue CTA (70.5%; 95% CI 59.1% to 80.3%), since the F1LCDx failed to detect a significant proportion of the patients, a reflex testing using tissue specimens to an FDA approved tissue test will be required, if feasible, if the plasma test is negative.

There are no studies directly assessing the clinical utility of FoundationOne Liquid to detect MET Exon 14 skipping alterations to select patients for targeted treatment.

Section Summary

The clinical validity of FoundationOne liquid was assessed in 1 clinical bridging study that compared FoundationOne Liquid to tissue testing using data from a nonrandomized, open-label, phase 2 study of capmatinib therapy. A chain of evidence demonstrates that testing strategy with FoundationOne CDx should produce outcomes similar to tissue testing. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity.

Section Summary: Clinically Useful

There is little evidence on the comparative validity of tissue and liquid biopsies in discordant cases for *EGFR* TKI-sensitizing variants. Based on the apparent response to *EGFR* TKIs in patients with negative liquid biopsies and positive tissue biopsies in the FDA approval study, these results are consistent with false-negative liquid biopsies. It is unclear whether false-positive liquid biopsies represent errors in the liquid biopsy or inadequacies of a tissue biopsy reference standard. In 1 study, 3 patients with negative tissue biopsies but positive liquid biopsies for biomarkers indicating *EGFR* TKI sensitivity had apparent responses to *EGFR* TKIs, consistent with the tissue biopsies being incorrectly negative.

A chain of evidence based on the sensitivity and specificity of liquid biopsy for the detection of *EGFR* TKI-sensitizing variants for tests with established clinical validity such as the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision can support its utility. The body of evidence has demonstrated moderate sensitivity (>63%), with high specificities (>96%). If a liquid biopsy is used to detect *EGFR* TKI-sensitizing variants with reflex testing of tissue samples in those with negative liquid biopsies, then the sensitivity of the testing strategy will be equivalent to tissue biopsy, and the specificity will be high. Therefore, outcomes should be similar, but tissue testing of biomarkers would be avoided in approximately two-thirds to three-quarters of patients with *EGFR* TKI-sensitizing variants.

For the other marketed tests that include detection of *EGFR* TKI-sensitizing variants and for liquid biopsy testing of other driver mutations, sufficient evidence of clinical validity is lacking, and thus a chain of evidence cannot be linked to support a conclusion that results for other ctDNA test methods will be similar to those for tissue biopsy.

For *EGFR* TKI-resistance variants, there is little evidence on the comparative validity of tissue and liquid biopsies in discordant cases. Based on the apparent response to osimertinib from the AURA and AURA3 studies with liquid-negative, tissue-positive results, these results are more consistent with false-negative liquid biopsies. In the AURA3 trial, patients with liquid-positive tests were associated with increased disease burden and increased plasma test sensitivity compared to liquid-negative patients. It is unclear whether false-positive liquid biopsies represent errors in the liquid biopsy or inadequacies of a tissue biopsy reference standard. In 3 studies, patients with negative tissue biopsies and positive liquid biopsies appeared not to have a high response to osimertinib or rociletinib. Sample sizes are very small for this scenario of discordance. Although the evidence is limited, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by the American Society of Clinical Oncology with an expert consensus opinion that "Physicians may use plasma ctDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to *EGFR* targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative." The National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, plasma-based testing should be considered and when plasma-based testing is negative, tissue-based testing is strongly recommended.

For tests of other, less prevalent, variants, such as *ALK* translocations, *ROS1* translocations, *RET* fusions, *MET* exon 14 skipping, and *BRAF* V600E variants, few studies were identified that evaluated the clinical validity of any commercially available tests and in these studies, very few variants were detected; therefore, performance characteristics are not well characterized. Because sufficient evidence of clinical validity is lacking, a chain of evidence cannot be linked to support the conclusion that results for other variants using ctDNA test methods will be similar to those for tissue biopsy.

Summary of Evidence
For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *EGFR* variants and *ALK* rearrangements, the evidence includes phase 3 studies comparing TKIs (e.g., afatinib, erlotinib, gefitinib, osimertinib, et al) with chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and PFS, with a reduction in toxicity and improvement in QOL. The evidence is sufficient to determine that the technology results in an 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. 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. In an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the ORR was 77%, with a median duration of response of 24.6 months and acceptable toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *RET* or *MET* gene testing, the evidence includes nonrandomized trials of kinase inhibitors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown efficacy in PFS and duration of response for selpercatinib and pralsetinib in patients with RET-fusion positive NSCLC, and for capmatinib in patients with *MET* Exon 14 skipping alterations, with acceptable toxicity. The evidence is sufficient to determine that the technology results in an 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* as a technique to predict treatment nonresponse to anti-EGFR therapy with TKIs or testing for *HER2* variants to select the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux), the evidence includes post hoc analysis of trials, observational studies, and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although 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 *KRAS* testing beyond *EGFR* testing. In 2 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. Studies for *HER2* 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 that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for *KRAS* to select targeted treatment, the evidence includes a phase 2, open-label trial of sotorasib in patients with KRAS variant NSCLC. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Presence of the KRAS alteration in tissue was confirmed on central laboratory testing with the use of the Therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% CI, 6.9 to not evaluable). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive NTRK gene fusion testing, the evidence includes nonrandomized trials of larotrectinib and entrectinib in patients with solid tumors. 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 who received larotrectinib, including 4 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. In an integrated analysis of 3 phase 1-2 trials in patients with NTRK solid tumors who received entrectinib, 10 of whom had NSCLC, response was 57% (95% CI, 43.2% to 70.8%) with an acceptable safety profile. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive PD-L1 testing, the evidence includes RCTs comparing immunotherapy to chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive TMB testing, the evidence includes a RCT and retrospective observational studies. In a subgroup analysis of the KEYNOTE trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among

patients with NSCLC and a high TMB (≥10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. Additionally, there is no consensus on how to measure TMB. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with the cobas EGFR Mutation Test v2 (liquid biopsy), the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are OS, disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of cobas. The cobas EGFR Mutation Test has adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. The U.S. Food and Drug Administration has suggested that a strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the cobas test would result in an overall diagnostic performance equivalent to tissue biopsy. Several additional studies of the clinical validity of cobas have shown it to be moderately sensitive and highly specific compared with a reference standard of tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the cobas test should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. The cobas test can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA (liquid biopsy) with the Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are OS, disease-specific survival, and test validity. Current evidence does not permit determining whether liquid or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of these tests. The Guardant360 CDx, OncoBEAM, and InVision tests have adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. A strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the tests would result in an overall diagnostic performance similar to tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the Guardant360 CDx, OncoBEAM, or InVision tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The

evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who have advanced-stage NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests other than the cobas, Guardant360 CDx, OncoBEAM, and InVision tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing using FoundationOne Liquid CDx, the evidence has demonstrated to be non-inferior to the cobas EGFR Mutation Test v2 (liquid biopsy) test for the detection of EGFR exon 19 deletions and EGFR exon 21 L858R mutations in metastatic non-small cell lung cancer (NSCLC). The studies completed establish the clinical validity of the FoundationOne Liquid CDx assay for identifying patients eligible for treatment with erlotinib, gefitinib, and osimertinib. For patients who cannot undergo tissue biopsy FoundationOne Liquid CDx test can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers other than *EGFR* using a liquid biopsy to select a targeted therapy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with the tissue biopsy reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for variants other than *EGFR*. We found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on *EGFR* TKIs who receive testing for biomarkers of *EGFR* TKI resistance using liquid biopsy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. For variants that

indicate *EGFR* TKI resistance and suitability for alternative treatments with osimertinib, liquid biopsy is moderately sensitive and moderately specific compared with a reference standard of tissue biopsy. Given the moderate clinical sensitivity and specificity of liquid biopsy, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for *EGFR* TKI resistance. It cannot be determined whether patient outcomes are improved. However, although there is higher discordance in the liquid versus tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Although the evidence is limited, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by the American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify *EGFR* T790M variants in patients with progression or resistance to *EGFR*-targeted TKIs and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib, or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered and when a liquid biopsy is negative tissue-based testing is strongly recommended.

Practice Guideline and Position Statements

American Society of Clinical Oncology (ASCO)
In 2017, the American Society of Clinical Oncology (ASCO) issued a guideline on systemic therapy for stage IV non-small cell lung cancer which included the following recommendations:

New or revised recommendations include the following. Regarding first-line treatment for patients with non–squamous cell carcinoma or squamous cell carcinoma (without positive markers, i.e., 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. All other clinical scenarios follow 2015 recommendations. 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. All immune checkpoint therapy is recommended alone plus in the absence of contraindications. For patients who received a prior first line immune checkpoint inhibitor, clinicians should offer standard chemotherapy. For patients who cannot receive immune checkpoint inhibitor after chemotherapy, docetaxel is recommended; in patients with non-squamous NSCLC, pemetrexed is recommended. In patients with a sensitizing EGFR mutation, disease progression after first-line epidermal growth factor receptor tyrosine kinase

inhibitor therapy, and T790M mutation, osimertinib is recommended; if NSCLC lacks the T790M mutation, then chemotherapy is recommended. Patients with ROS1 gene rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

Recommendations

First-Line Treatment for Patients

- Patients with non–squamous cell carcinoma without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with a performance status (PS) of 0 or 1 (and appropriate PS of 2):
- With high PD-L1 expression (tumor proportion score [TPS] 50%) and no contraindications, single-agent pembrolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
- With low PD-L1 expression (TPS, 50%), a variety of combination cytotoxic chemotherapies (with or without bevacizumab if patients are receiving carboplatin and paclitaxel) are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: intermediate; Strength of recommendation: weak]).
- There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin.
- Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.
- With PS of 2, combination or single-agent therapy or palliative care alone may be used (chemotherapy [Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Evidence quality: intermediate; Strength of recommendation: strong]).

Patients with squamous cell carcinoma without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with a PS of 0 or 1 (and appropriate PS of 2):

- With high PD-L1 expression (TPS 50%) and no contraindications, single-agent pembrolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
- With low PD-L1 expression (TPS, 50%), a variety of combination cytotoxic chemotherapies are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: low; Strength of recommendation: weak]).
- Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.

With PS of 2, combination or single-agent therapy or palliative care alone may be used (chemotherapy [Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Evidence quality: intermediate; Strength of recommendation: strong]).

- With squamous NSCLC treated with cisplatin and gemcitabine, the Panel neither recommends for nor recommends against the addition of necitumumab to chemotherapy.
- With sensitizing EGFR mutations, afatinib, erlotinib, or gefitinib is recommended (Evidence quality: high; Strength of recommendation: strong for each).

- With ALK gene rearrangements, crizotinib is recommended (Evidence quality: strong; Strength of recommendation: high).
- With ROS1 rearrangement, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Second-Line Treatment for Patients

Without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with PS of 0 or 1 (and appropriate PS of 2):

- In patients with high PD-L1 expression (TPS, 1%) and no contraindications who received first-line chemotherapy and have not received prior immune therapy, single-agent nivolumab, pembrolizumab, or atezolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
- In patients with negative or unknown tumor PD-L1 expression (TPS, 1%) and no contraindications who received first-line chemotherapy, nivolumab, or atezolizumab, a variety of combination cytotoxic chemotherapies are recommended (Evidence quality: high; Strength of recommendation: strong).
- Other checkpoint inhibitors, combination checkpoint inhibitors, and immune checkpoint therapy with chemotherapy are not recommended.
- In patients who received an immune checkpoint inhibitor as first-line therapy, a variety of combination cytotoxic chemotherapies are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong].

Non–platinum based [Informal consensus; Evidence quality: low; Strength of recommendation: strong]).

- In patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended (Evidence quality: intermediate; Strength of recommendation: moderate).
- In patients with non–squamous cell carcinoma who have not previously received pemetrexed, pemetrexed is recommended (Evidence quality: intermediate; Strength of recommendation: moderate).

With sensitizing EGFR mutations:

- In patients with disease progression after first-line therapy with an EGFR tyrosine kinase inhibitor (TKI) and the presence of the T790M resistance mutation, osimertinib is recommended (Evidence quality: high; Strength of recommendation: strong).
- If T790Mmutation is not present, a platinumdoublet is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).
- In patients who received an EGFR-TKI in the first-line setting, had an initial response, and subsequently experienced slow or minimal disease progression at isolated sites, EGFR-TKI with local therapy to the isolated sites is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

With ROS1 rearrangement:

- In patients who have not received prior crizotinib, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- In patients who have received prior crizotinib, platinum-based therapy in the second line with or without bevacizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

With BRAF mutations:

- In patients without prior immune checkpoint therapy and high PD-L1 expression (TPS, 1%), atezolizumab, nivolumab, or pembrolizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).
- In patients who have received prior immune checkpoint therapy, dabrafenib alone or in combination with trametinib in third line is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Third-Line Treatment for Patients

- In patients without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with non–squamous cell carcinoma and PS of 0 or 1 (and appropriate PS of 2), who received chemotherapy with or without bevacizumab and immune checkpoint therapy, single-agent pemetrexed or docetaxel are options (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).
- In patients with tumor EGFR-sensitizing mutation(s) who have received at least one first-line EGFR-TKI and prior platinum-based chemotherapy, there are insufficient data to recommend immunotherapy in preference to chemotherapy (pemetrexed or docetaxel [Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak])**.**

Fourth-Line Treatment for Patients

- Patients and clinicians should consider and discuss experimental treatment, clinical trials, and continued best supportive **(**palliative) care.

In 2018, the American Society of Clinical Oncology (ASCO) Expert Panel determined that the recommendations from the College of American Pathologists (CAP)/ the International Association for the Study of Lung Cancer (IASLC)/the Association for Molecular Pathology (AMP) molecular testing guideline are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the guideline with minor modifications.

Target Population

Patients with advanced lung cancer (i.e., stage IV or other incurable lung cancer).

Target Audience
Medical or surgical oncologists, pathologists, thoracic surgeons, and specialists in pulmonary medicine or interventional radiology.

Key Recommendations
2013 Recommendations that were reaffirmed or updated for 2018:

1. Expert Consensus Opinion: Pathologists may use either cell blocks or smear preparations as suitable specimens for lung cancer biomarker molecular testing.
2. Expert Consensus Opinion: Laboratories should use, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells.
3. Strong Recommendation: Laboratories should not use epidermal growth factor receptor (EGFR) expression by immunohistochemistry (IHC) testing to select patients for EGFR-targeted TKI therapy.
4. Recommendation: Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.
5. Recommendation: Pathologists and laboratories should not use EGFR copy number analysis (i.e., fluorescent in situ hybridization or chemiluminescent in situ hybridization) to select patients for EGFR-targeted TKI therapy.

New 2018 Recommendations:
Key Question 1: Which genes should be tested for patients with lung cancer?

1. Recommendation: ROS1 testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
2. Expert Consensus Opinion: ROS1 IHC may be used as a screening test in patients with advanced lung adenocarcinoma; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.
3. Expert Consensus Opinion: BRAF testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
4. Expert Consensus Opinion: RET molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include RET as part of larger testing panels performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative.
5. Expert Consensus Opinion: ERBB2 (HER2) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include ERBB2 (HER2) mutation analysis as part of a larger testing panel performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative.
6. Expert Consensus Opinion: 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, BRAF, and ROS1 testing is negative.

7. Expert Consensus Opinion: MET molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include MET as part of larger testing panels performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative.

Key Question 2: What methods should be used to perform molecular testing?

8. Recommendation: IHC is an equivalent alternative to FISH for ALK testing.

CAP/IASLC/AMP Qualifying Statement: *ALK IHC is an acceptable standard alternative to FISH, and treatment decisions can be made when IHC results are clearly positive, as manifested by strong granular cytoplasmic staining, with or without membrane accentuation, or negative; however, weak staining can be challenging to interpret, and the specificity of weak staining relative to FISH should be determined in each laboratory during validation.*

9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred where available over multiple single gene tests to identify other treatment options beyond EGFR, ALK, BRAF, and ROS1.
10. Expert Consensus Opinion: Laboratories should ensure that test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved by using an alternative method or sample.

Key Question 3: Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?

11. Expert Consensus Opinion: Physicians may use molecular biomarker testing in tumors with:
    a. an adenocarcinoma component
    b. non-squamous, non–small-cell histology
    c. any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver *(e.g., young age [, 50 years]; light or absent tobacco exposure).*

Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?

12. Strong Recommendation: In patients with lung adenocarcinoma who harbor sensitizing EGFR mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use EGFR T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.
13. Recommendation: 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.
14. No Recommendation: There is currently insufficient evidence to support a recommendation for or against routine testing for ALK mutational status for patients with lung adenocarcinoma with sensitizing ALK mutations who have progressed after treatment with an ALK-targeted TKI.

Key Question 5: What is the role of testing for circulating cell-free DNA (cfDNA) for patients with lung cancer?

15. No Recommendation: There is currently insufficient evidence to support the use of cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma.
16. Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations.
17. Expert Consensus Opinion: Physicians may use cfDNA methods to identify EGFR T790M mutations in patients with lung adenocarcinoma who have progression or secondary clinical resistance to EGFR-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative.
18. No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of EGFR T790M mutations at the time of EGFR TKI resistance.

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

In 2018, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC) and the Association for Molecular Pathology (AMP) updated their molecular testing guidelines for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors.

Key Question 1: Which new genes should be tested for lung cancer patients?

	Guideline Statement	Strength of Recommendation
1.	*ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics.	Strong Recommendation
2.	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.	Expert Consensus Opinion
3.	*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.	Expert Consensus Opinion
4.	*RET* molecular testing is not recommended as a routine stand-alone assay outside the context	Expert Consensus Opinion

	of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are negative.	
5.	*ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR, ALK*, and *ROS1* testing are negative.	Expert Consensus Opinion
6.	*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.	Expert Consensus Opinion
7.	*MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK,* and *ROS1* testing are negative.	Expert Consensus Opinion

Key Question 2: What methods should be used to perform molecular testing?

	Guideline Statement	**Strength of Recommendation**
8.	IHC is an equivalent alternative to FISH for ALK testing.	Recommendation
9.	Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK*, and *ROS1*.	Expert Consensus Opinion
10.	Laboratories should ensure test results that are unexpected, discordant, equivocal, or otherwise of low confidence are confirmed or resolved using an alternative method or sample.	Expert Consensus Opinion

Key Question 3: Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?

	Guideline Statement	Strength of Recommendation
11.	Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.	Expert Consensus Opinion

Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?

	Guideline Statement	Strength of Recommendation
12	In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use *EGFR* T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.	Strong Recommendation
13.	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.	Recommendation
14.	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 TKI.	No Recommendation

Key Question 5: What is the role of testing for circulating cell-free DNA for lung cancer patients?

15.	There is currently insufficient evidence to support the use of circulating cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma.	No Recommendation
16.	In some clinical settings in which tissue is limited and/or insufficient for molecular	Recommendation

	testing, physicians may use a cfDNA assay to identify *EGFR* mutations.	
17.	Physicians may use cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKI; testing of the tumor sample is recommended if the plasma result is negative.	Expert Consensus Opinion
18.	There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI resistance.	No Recommendation

Abbreviations: ROS1, ROS Proto-Oncogene 1, Receptor Tyrosine Kinase; IHC, Immunohistochemistry; BRAF, B-Raf Proto-Oncogene, Serine/Threonine Kinase; EGFR, Epidermal Growth Factor Receptor; ALK, RET, Ret Proto-Oncogene; ERBB2, Erb-B2 Receptor Tyrosine Kinase 2; HER2, human epidermal growth factorreceptor 2; KRAS, MET, MET Proto-Oncogene, Receptor Tyrosine Kinase; FISH, fluorescence *in situ* hybridization; TKI, tyrosine kinase inhibitors; cfDNA, cell-free plasma DNA.

National Comprehensive Cancer Network (NCCN)

Non-Small Cell Lung Cancer Version 3.2022

Testing for Molecular Biomarkers
NCCN guidelines on NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines include the following recommendations and statements related to testing for molecular biomarkers:

- Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers.
- 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 potential genetic variants:
    - EGFR mutations
    - BRAF mutations
    - MET exon 14 skipping mutations
    - RET 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 NTRK gene fusions, high-level MET amplification, ERBB2 mutations, and TMB.
- Clinicopathologic features should not be used to select patients for testing
- The guidelines do not endorse any specific commercially available biomarker assays.

Plasma Cell-Free/Circulating Tumor DNA Testing

The NCCN guidelines on NSCLC include the following recommendations related to plasma cell-free/circulating tumor DNA testing.

- Plasma cell free/circulating tumor DNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC.
- Plasma cell free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis, but cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, notably:
    - If the patient is medically unfit for invasive tissue sampling; or
    - In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified.

The guidelines also state:

- Standards for analytic performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.

Regulatory Status

The table below summarizes FDA approved targeted treatment for NSCLC and along with the concurrently approved companion diagnostic tests. (Note this information is current as of August 2022. FDA maintains a list of cleared or approved companion diagnostics at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Afatinib (Gilotrif)	• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19	• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen)

	deletions or exon 21 (L858R) 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	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA
Alectinib (Alecensa)	• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Ventana ALK (D5F3) CDx Assay • 2020: FoundationOne Liquid CDx
Amivantamab-vmjw (Rybrenant)	• 2021: adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Guardant360 CDx
Atezolizumab (Tecentriq)	• 2020: First-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune	• 2020: VENTANA PD-L1

	cells covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations. o in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations o in combination with paclitaxel protein-bound and carboplatin for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations o for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemot herapy.	

Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib • 2020: Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2020: Vysis ALK Break Apart FISH Probe Kit • 2020: FoundationOneCDX
Capmatinib (Tabrecta)	• 2020: metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx (Foundation Medicine) • 2021: FoundationOne Liquid CDx
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) • 2017: VENTANA ALK (D5F3) CDx Assay
Crizotinib (Xalkori)	• 2011: First line for patients with ALK- or ROS1-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) • Oncomine Dx • 2017: VENTANA ALK (D5F3) CDx Assay
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	• 2018: therascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
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)
Entrectinib (Rozlytrek)	• 2019: o Adult patients with metastatic NSCLC whose tumors are ROS1-positive o Adult and pediatric patients	• No companion diagnostic

	12 years of age and older with ▪ solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, ▪ are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy	
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	• 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)

	cycles of platinum-based chemotherapy • 2004: Second line for patients with locally advanced or metastatic NSCLC	• 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
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) • 2017: Oncomine Dx Target Test • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Ipilimumab (Yervoy)	• Treatment of adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test,	• PD-L1 IHC 28-8 PharmDx

	with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab • Treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum doublet chemotherapy	
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that o have a 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	• FoundationOne CDx (solid tumors, NTRK1/2/3 fusions)
Lorlatinib (Lorbrena)	• 2018: Patients with ALK-positive metastatic	• No companion diagnostic

	NSCLC whose disease has progressed on: o crizotinib and at least 1 other ALK inhibitor for metastatic disease; or o alectinib as the first ALK inhibitor therapy for metastatic disease; or o ceritinib as the first ALK inhibitor therapy for metastatic disease	
Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)	• 2020: o adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab o adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with	• PD-L1 IHC 28-8 PharmDx

	ipilimumab and 2 cycles of platinum-doublet chemotherapy o patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	
Osimertinib (Tagrisso)	• 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by an FDA-approved test, who have not responded to EGFR-blocking therapy • 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants • 2019: EGFR exon 19 deletion and EGFR exon 21 L858R alterations • 2020: adjuvant therapy after tumor resection in	• 2015: cobas® EGFR Mutation Test v2 (blood test) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne® Liquid CDx

	adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test	
Pembrolizumab (Keytruda)	• 2018: Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA • 2020: For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	• 2018: PD-L1 IHC 22C3 pharmDx • 2020: FoundationOne CDx

Pralsetinib (Gavreto)	• Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• No companion diagnostic specified
Sotorasib (Lumakras)	• Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx
Tepotinib (Tepmetko)	• Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	• No companion diagnostic

ALK: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; MET: mesenchymal-epithelial transition; NSCLC: non-small-cell lung cancer; NTRK neurotrophic receptor tyrosine kinase; PCR: polymerase chain reaction.

PRIOR APPROVAL

Not Applicable

POLICY

See Related Medical Policies

- 02.04.16 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsies)
- 02.04.55 Epidermal Growth Factor Receptor (EGFR) Mutational Analysis Excluding Non-Small Cell Lung Cancer
- 02.04.20 KRAS/NRAS and BRAF Mutation Analysis
- 02.04.77 Proteomic Testing for Systematic Therapy in Non-Small Cell Lung Cancer

Biomarker Testing using Tissue Biopsy to Select Targeted Therapy

ALK Testing
Analysis of somatic rearrangements variants of anaplastic lymphoma kinase (*ALK*) gene using tumor tissue specimen (formalin-fixed paraffin-embedded tissue) may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [xalkori], ceritinib [zykadia], alectinib [alecensa], lorlatinib [lorbrena], or brigatinib [alunbrig]) in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small cell lung cancer (NSCLC), and non-small cell lung cancer (NSCLC) not otherwise specified.

Analysis for ALK rearrangements not meeting the above criteria and for all other indications is considered **not medically necessary.**

Analysis of somatic rearrangement variants of the ALK gene using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy *(see Policy Guidelines below)* to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with non-small cell lung cancer (NSCLC).

BRAF V600E Testing
Analysis of the somatic BRAF V600E variant using tumor tissue specimen (formalin-fixed paraffin-embedded tissue) may be considered **medically necessary** to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [tafinlar] and trametinib [mekinist]), in individuals with advanced non-small cell lung cancer (NSCLC) in whom an adenocarcinoma component cannot be excluded *(see Policy Guidelines section below)*.

Analysis for BRAF V600E variants not meeting the above criteria and for all other indications is considered **not medically necessary.**

Analysis of the somatic BRAF V600E variant using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy *(see Policy*

Guidelines below) to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar], trametinib [Mekinist]) in individuals with non-small cell lung cancer (NSCLC).

EGFR Testing
Analysis of somatic variants of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor *(EGFR)* gene, may be considered **medically necessary** to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in individuals with advanced non-small cell lung adenocarcinoma, large non-small cell lung carcinoma, advanced squamous-cell non-small cell lung cancer (NSCLC), and non-small cell lung cancer (NSCLC) not otherwise specified.

Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to non-small cell lung cancer (NSCLC), is considered **not medically necessary**.

At diagnosis, only analysis of somatic variants in exons 19 through 21 (e.g., exon 19 deletions, L858R, T790M) within the *EGFR* gene, using the cobas EGFR Mutation Test v2 using tissue may be considered **medically necessary** to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in patients with advanced non-small cell lung adenocarcinoma, large non-small cell carcinoma, advanced squamous cell non-small cell lung cancer (NSCLC), and non-small cell lung cancer (NSCLC) not otherwise specified.

At progression, analysis of the EGFR T790M resistance variant for targeted therapy with osimertinib (Tagrisso) using ctDNA using the cobas EGFR Mutation Test v2 tissue may be considered **medically necessary** in individuals with advanced non-small cell lung adenocarcinoma, large non-small cell carcinoma, advanced squamous cell non-small cell lung cancer (NSCLD), and non-small cell lung cancer (NSCLC) not otherwise specified.

For the diagnosis and progression analysis of exons 19 through 21 (e.g., exon 19 deletions, L858R, T790M) within the *EGFR* gene or EGFR T790M not meeting the above criteria is considered **not medically necessary**.

HER2 Testing
Analysis of somatic alterations in the *HER2* gene in tissue for targeted therapy in individuals with non-small cell lung cancer (NSCLC) is considered **not medically necessary.**

Analysis of somatic alterations in the HER2 gene using plasma specimens to detect ctDNA for targeted therapy in individuals with non-small cell cancer (NSCLC) is considered **not medically necessary.**

KRAS Testing
Analysis of somatic variants of the *KRAS* gene in tissue may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) in individuals with advanced non-small cell lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis for KRAS variants not meeting the above criteria and for all other indications is considered **not medically necessary.**

Analysis of somatic variants of the KRAS gene using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy to predict treatment response to sotorasib (Lumakras). *(See Policy Guidelines below)*

MET Exon 14 Skipping Alteration
Analysis of somatic alteration in tissue that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) in individuals with metastatic non-small cell lung cancer (NSCLC).

Analysis for *MET* exon 14 skipping not meeting the above criteria and for all other indications is considered **not medically necessary.**

Analysis of somatic alteration that leads to *MET* exon 14 skipping using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy *(see Policy Guidelines below)* to predict treatment response to MET inhibitor therapy (capmatinib [Tabrecta]) in individuals with non-small cell lung cancer (NSCLC).

NTRK Gene Fusion Testing
Analysis of somatic *NTRK* gene fusions in tissue may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or 74arotrectinib (Vitrakvi) in individuals with advanced non-small cell lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis for somatic *NTRK* gene fusions not meeting the above criteria and for all other indications is considered **not medically necessary.**

Analysis of somatic *NTRK* gene fusions using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy *(see Policy Guidelines below)* to predict treatment response to entrectinib (Rozlytrek) or arotrectinib (Vitrakvi) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

PD-L1 Expression Testing
Testing for PD-L1 expression using tumor tissue specimen (formalin-fixed paraffin-embedded tissue) in an individual diagnosed with metastatic non-small cell lung cancer

(NSCLC) is considered **medically necessary** to predict response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in individuals with metastatic non-small cell lung cancer (NSCLC).

Testing for PD-L1 expression by immunohistochemistry not meeting the above criteria and for all other indications is considered **not medically necessary.**

Testing for PD-L1 expression by immunohistochemistry using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy *(see Policy Guidelines below)* to predict response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in individuals with metastatic non-small cell lung cancer (NSCLC).

RET Rearrangement Testing
Analysis of somatic alteration in the *RET* gene in tissue may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic non-small cell lung cancer (NSCLC).

Analysis of somatic alterations in the RET gene is considered **not medically necessary** not meeting the above criteria and for all other indications.

Analysis of somatic alterations in RET gene using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy to predict treatment response to RET inhibitor therapy (e.g., selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with metastatic non-smal cell lung cancer NSCLC.

ROS1 Testing
Analysis of somatic rearrangement variants of the ROS1 gene in tissue may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded *(see Policy Guidelines section)*.

Analysis of somatic alterations in the ROS1 gene is considered **not medically necessary** not meeting the above criteria and for all other indications.

Analysis of somatic rearrangement variants of the ROS1 gene using plasma specimens to detect ctDNA is considered **not medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in individuals with non-small cell lung cancer (NSCLC).

Tumor Mutations Burden (TMB)
Analysis of tumor mutational burden (TMB) using tumor tissue specimen (formalin-fixed paraffin-embedded tissue) or using ctDNA as an alternative to tissue biopsy is considered

not medically necessary individuals with non-small cell lung cancer (NSCLC) to determine targeted therapy.

Biomarker Testing using Plasma Testing (Liquid Biopsy) to Select Targeted Therapy

Plasma testing (liquid biopsy ctDNA) (cobas EGFR Mutation Test v2, Guardant360, Guardant360 CDx, Guardant360 Tissue Next, FoundationOne Liquid CDx, InvisionFirst-Lung, or OncoBeam) for oncogenic driver variants deemed medically necessary on tissue biopsy (above) may be considered **medically necessary** to predict treatment response to targeted therapy for individuals meeting **ALL** the following criteria:

- Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; **or**
- Individual does not have a biopsy amendable lesion; **or**
- Individual cannot undergo biopsy; **and**
- Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing (liquid biopsy ctDNA).

Plasma testing (liquid biopsy ctDNA) (cobas EGFR Mutation Test v2, Guardant360, Guardant360 CDx, Guardant360 Tissue Next, FoundationOne Liquid CDx, InvisionFirst-Lung, or OncoBeam) for oncogenic driver variants not meeting the above criteria is considered **not medically necessary.**

The following plasma testing (liquid biopsy ctDNA) including but not limited to the following to predict treatment response of targeted therapy in the treatment of metastatic non-small cell lung cancer (NSCLC) is considered **investigational**, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Circulogene's Liquid Biopsy Test
- ClearID Biomarker Expression Assays
- ClearID Lung Cancer
- ctDX Lung
- GeneStrat now known as Biodesix ddPCR
- LiquidGX
- Oncomine DX Target Test for Lung
- PlasmaSelect 64
- Resolution ctDx Lung Assay
- Signatera Lung
- Target Selector
- Tempus xF Liquid Biopsy Panel

Other Single Genes Related to Non-Small Cell Lung Cancer

Testing for the following genomic biomarkers using tumor tissue specimen (formalin-fixed paraffin-embedded tissue) to predict treatment response of targeted therapy in the treatment of metastatic non-small cell lung cancer (NCSLC) as an **individual** biomarker marker, including but not limited to the following, is considered **investigational,** because

the evidence is insufficient to determine the effects of the technology on net health outcomes and based on current society guidelines these genetic variants are currently not identified as gene alterations that impact targeted therapy selections for metastatic non-small cell lung cancer (NSCLC):

- AKT1
- APC Sequencing
- AR
- ARAF
- ARID1A
- ATM
- CCND1
- CCND2
- CCNE1
- CDH1
- CDK4
- CDK6
- CDKN2A
- CTNNB1
- DDR2
- ESR1
- E2H2
- FBXW7
- FGFR1
- FGFR2
- FGFR3
- GATA3
- GNA11
- GNAQ
- GNAS
- HNF1A
- HRAS
- IDH1
- IDH2
- JAK2
- JAK3
- KIT
- MAP2K1/MEK1
- MAP2K2/MEK2
- MAPK1/ERK2
- MAPK3/ERK1
- Microsatellite instability analysis
- MLH1
- MPL

- MSH2
- MSH6
- MTOR
- MYC
- NF1
- NFE2L2
- NOTCH1
- NPM1
- NRAS
- PDGFRA
- PIK3CA
- PMS2
- PTEN
- PTPN11
- RAF1
- RB1
- RHEB
- RHOA
- RIT1
- SMAD4
- SMO
- STK11
- TERT
- TP53
- SCI1
- VHL

Policy Guidelines

These gene tests are intended for use in individuals with advanced (stage III or IV) non-small-cell lung cancer (NSCLC). Individuals with either small deletions in exon 19 or a point mutation 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. Individuals with wild-type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered.

Guidelines from the National Comprehensive Cancer Network (NCCN) on non-small-cell lung (NCSLC) cancer provide recommendations for biomarker testing. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (3.2022) recommend that *EGFR* variants, *ALK* rearrangement, and PD-L1 testing (category 1) as well as *KRAS*, *ROS1*, *BRAF, NTRK1/2/3, MET* Exon 14 skipping alteration, and *RET* 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 guidelines add that testing should be conducted as part of broad molecular profiling.

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."

The tests discussed herein, cobas EGFR Mutation Test v2, Guardant360, Guardant360 CDx, Guardant360 Tissue Next, FoundationOne Liquid CDx, InvisionFirst-Lung, or OncoBeam), are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. These tests include variants beyond exons 19 through 21 of the epidermal growth factor receptor (*EGFR)* gene, and some tests additionally include variants in numerous other genes. Patients with sensitizing variants of the tyrosine kinase domain of the *EGFR* gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib. The U.S. Food and Drug Administration approval for the cobas EGFR Mutation Test v2 states that patients who are negative for *EGFR* exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. Plasma tests for other oncogenic driver variants deemed medically necessary on tissue biopsy may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; however, this is only appropriate if follow-up tissue-based analysis is planned should no driver variant be identified.

Recommended Testing Strategies
Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81120 IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (e.g., glioma), common variants (e.g., R132H, R132C)
- 81121 IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (e.g., glioma), common variants (e.g., R140W, R172M)
- 81173 AR (androgen receptor) (e.g., spinal, and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
- 81191 NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
- 81192 NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
- 81193 NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
- 81194 NTRK (neurotrophic receptor tyrosine kinase 1. 2. 3) (e.g., solid tumors) translocation analysis
- 81201 APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
- 81210 BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
- 81235 EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
- 81270 JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
- 81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)
- 81275 KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
- 81276 KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
- 81277 Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
- 81279 JAK2 (Janus Kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)
- 81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

- 81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81298 MSH6 (mutS homolog 2, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81301 Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- 81310 NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants
- 81311 NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
- 81314 PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g., gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (e.g., exons 12,18)
- 81317 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81321 PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
- 81400 Molecular pathology procedure, level 1
- 81401 Molecular pathology procedure level 2 (includes EML4/ALK)
- 81402 Molecular pathology procedure, level 3
- 81403 Molecular pathology procedure, level 4
- 81404 Molecular pathology procedure, level 5 (includes RET)
- 81405 Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) (e.g., includes full sequence RET [ret proto-oncogene]) (e.g., multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma)
- 81406 Molecular pathology procedure, Level 7
- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or

rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

- 81479 Unlisted molecular pathology procedure
- 86152 Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)
- 86153 Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
- 88360 Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
- 88361 Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
- 0022U Targeted genomic sequence analysis panel, cholangiocarcinoma and non-small cell lung neoplasia, DNA and RNA analysis, 1-23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider (Oncomine DX Target Test)
- 0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (FoundationOne CDx [F1CDx])
- 0179U Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s) (Resolution ctDx Lung Assay)
- 0239U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne Liquid CDx)
- 0242U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements (Guardant360 CDx)
- 0326U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Guardant360)
- 0034U Oncology (solid organ) targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFEP) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Gaurdant360 Tissue Next)

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POLICY HISTORY

Date	Reason	Action
September 2022	Annual Review	Policy Revised Content moved from medical policy Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy) and combined with this medical policy
November 2021	Interim Review	Policy Revised
September 2021	Annual Review	Policy Revised

September 2020	Annual Review	Policy Revised
September 2019		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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