

Medicare Advantage Medical Policy



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Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy) – Medicare Advantage

Medicare Advantage Plan

☒ Medicare Plus BlueSM

☒ BCN AdvantageSM

UM Committee Approval Date: 9/17/2025

Effective Date: 10/17/2025

Description

A liquid biopsy is a minimally invasive diagnostic test that involves the analysis of circulating tumor DNA (ctDNA) fragments, which are shed by cancer cells into the bloodstream or other bodily fluids, such as plasma, serum, or urine. In the context of non-small-cell lung cancer (NSCLC), liquid biopsy utilizes advanced molecular technologies, including next-generation sequencing (NGS) and polymerase chain reaction (PCR), to detect and analyze specific genetic mutations, such as EGFR, KRAS, BRAF, and others. These mutations have been purported to provide insights into the molecular characteristics of the tumor, enabling personalized treatment approaches and monitoring of disease progression.

Related Medical Coverage Policies

- Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
 - Genetic Testing - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
 - Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer (NSCLC), e.g., VeriStrat®
 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
 - Genetic Testing – NGS of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions
 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
 - Miscellaneous Genetic and Molecular Diagnostic Tests
 - Genetic Testing and Counseling
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Policy Guidelines

Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network of Michigan (BCN) adhere to guidance from the Centers for Medicare and Medicaid Services (CMS), including when performing organization determinations for Medicare Advantage plan members. CMS Medicare statutes, regulations, manuals, National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and other sub-regulatory guidance provide the clinical guidelines for coverage determinations, payment integrity functions, and all other uses by CMS regulations. When CMS Medicare guidance is not fully established, CMS permits BCBSM/BCN to utilize “internal coverage criteria”, such as independent criteria, health plan policy research, LCD/LCAs outside the services area or research from independent medical research repositories (i.e., Hayes) for coverage policies 42 CFR § 422.101. BCBSM/BCN internal medical coverage policies are developed and based on current evidence in widely accepted treatment guidelines or clinical literature; in addition, they address how clinical benefits may or may not outweigh member harm.

The following are applicable for this medical policy:

After searching the Medicare Coverage Database and other sources of conditions of coverage, it was determined that CMS guidance to determine medical necessity is not fully developed related to codes found in this medical policy. BCBSM/BCN internal coverage criteria will only be applied where CMS guidance is silent. This service may be medically necessary when the criteria are met.

Code	Description	NCD/LCD/LCA	Additional Guidance
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis	National Coverage Determinations NCD: 90.2 Next Generation Sequencing (NGS)	When the NCDs, LCDs, or LCAs do not have fully established clinical coverage criteria to determine medical necessity for Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)—Medicare Advantage refer to the BCBSM/BCN policy: <i>Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)</i> Policy attached below
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis	Local Coverage Determinations WPS L36807, A57772 – MoIDX: Molecular Diagnostic Tests (MDT)*	
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis	L38168, A57935 – MoIDX: Plasma-Based Genomic Profiling in Solid Tumors*	
81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis	L39040, A58756 - MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer* L38158, A57858 – MoIDX: Next-Generation Sequencing for Solid Tumors*	
81210	BRAF (B-Raf proto-oncogene, serine/ threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)	A55197 – Billing and Coding: MoIDX: Targeted and Comprehensive Genomic Profile Testing in Cancer* L38684, A58211 – MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer*	
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)	L38835 - MoIDX: Minimal Residual Disease Testing for Cancer* A58468 – Billing and Coding: MoIDX: Minimal Residual Disease Testing for Solid Tumor Cancers*	

Code	Description	NCD/LCD/LCA	Additional Guidance
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)	A55161 – Billing and Coding: MoIDX: FDA-Approved BRAF Tests* A55162 – Billing and Coding: MoIDX: FDA-Approved KRAS Tests*	
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)	CGS L36021, A56973 - MoIDX: Molecular Diagnostic Tests (MDT)* L38065, A57917 – MoIDX: Plasma-Based Genomic Profiling in Solid Tumors* L39017, A58734 - MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer* L38067, A57870 – MoIDX: Next-Generation Sequencing for Solid Tumors* L38586, A58065 – MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer* L38822 - MoIDX: Minimal Residual Disease Testing for Cancer* A58434 – Billing and Coding: MoIDX: Minimal Residual Disease Testing for Solid Tumor Cancers*	
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [Includes: EML4/ALK (inv(2)) (e.g., non-small cell lung cancer), translocation or inversion analysis]	A54191 - Billing and Coding: MoIDX: FDA-Approved BRAF Tests* A54688 – Billing and Coding: MoIDX: FDA-Approved KRAS Tests*	
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [use for RET (ret proto-oncogene)]	First Coast L34519, A57451 - Molecular Pathology Procedures A58918 - Billing and Coding: Molecular Pathology and Genetic Testing [Not an LCD reference model article]	
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) (use for RET targeted sequence analysis)	NGS L37810, A56867 – Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms L35000, A56199 - Molecular Pathology Procedures Noridian JE and JF L35160, A57526 - MoIDX: Molecular Diagnostic Tests (MDT)* L39230, A58973 – MoIDX: Plasma-Based Genomic Profiling in Solid Tumors* L38972, A58679 - MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer*	
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis)		

Code	Description	NCD/LCD/LCA	Additional Guidance
	for neoplasia) (use for BRAF analysis)	L38119, A57901 – MoIDX: Next-Generation Sequencing for Solid Tumors*	
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	A55624 – Billing and Coding: MoIDX: Targeted and Comprehensive Genomic Profile Testing in Cancer* L38647, A58181 – MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer* L38814 - MoIDX: Minimal Residual Disease Testing for Cancer*	
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, 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	A58454 – Billing and Coding: MoIDX: Minimal Residual Disease Testing for Solid Tumor Cancers* A54418 - Billing and Coding: MoIDX: FDA-Approved BRAF Tests* A54498 – Billing and Coding: MoIDX: FDA-Approved KRAS Tests* Novitas L35396, A52986 – Biomarkers for Oncology L35062, A56541 – Biomarkers Overview	
81479	Unlisted molecular pathology procedure	A58917 – Billing and Coding: Molecular Pathology and Genetic Testing	
88346	Immunofluorescence, per specimen; initial single antibody stain procedure	Palmetto L36256, A57527 - MoIDX: Molecular Diagnostic Tests (MDT)*	
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)	L38043, A57867 – MoIDX: Plasma-Based Genomic Profiling in Solid Tumors* L38966, A58652 MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer*	
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™, Resolution Bioscience, Inc. Laboratory in WA]	L38045, A57831 – MoIDX: Next-Generation Sequencing for Solid Tumors* A54795 – Billing and Coding: MoIDX: Targeted and Comprehensive Genomic Profile Testing in Cancer* L38576, A58028 – MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer* L38779 - MoIDX: Minimal Residual Disease Testing for Cancer*	
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including	A58376 – Billing and Coding: MoIDX: Minimal Residual Disease Testing for Solid Tumor Cancers* A54018 – Billing and Coding: MoIDX: FDA-Approved BRAF Tests*	

Code	Description	NCD/LCD/LCA	Additional Guidance
	substitutions, insertions, deletions, select rearrangements, and copy number variations [FoundationOne® Liquid CDx, Foundation Medicine, Inc. Laboratories in MA, NC, and CA]	A54472 – Billing and Coding: MoIDX: FDA-Approved KRAS Tests*	
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, Guardant Health Inc. Laboratories in CA]		
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®, Guardant Health Inc. Laboratories in CA]		
0530U	Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy-number alterations, with therapy association [LiquidHALLMARK®, Lucence Health, Inc. Laboratory in CA]		

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* MoIDX® Program (Administered by Palmetto GBA): The following MACs have implemented the MoIDX program: WPS, CGS, Noridian, Palmetto. The MoIDX Program was developed to identify and establish coverage and reimbursement for molecular diagnostic tests. The MoIDX evaluates genetic tests to determine analytical and clinical validity and clinical utility, as well as confirming that each test meets Medicare criteria. Please refer to the MoIDX® website <https://www.palmettogba.com/MoIDX> for covered and excluded tests' specific coding and

billing information. For additional information regarding what tests will fall into a Medicare benefit category or which tests are statutory excluded (e.g., predictive, prenatal, and carrier testing and tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law) please refer to <https://www.palmettogba.com/palmetto/moldxv2.nsf/DID/DPR5GEM991>

The above information is current as of the review date for this policy. However, the coverage issues and policies maintained by CMS are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. Please refer to the Medicare Coverage Database website at <https://www.cms.gov/medicare-coverage-database/search.aspx> for the most current applicable NCD, LCD, LCA, and CMS Online Manual System Transmittals.

CMS Medicare Administrative Contractors (MAC) Jurisdictions

Part A and Part B Medicare Administrative Contractor (MAC) Jurisdiction	
Wisconsin Physicians Service Insurance Corporation (WPS)	IA, IN, KS, MI, MO, NE
CGS Administrators, LLC	KY, OH
First Coast Service Options, Inc	FL, PR, US VI
National Government Services, Inc (NGS)	CT, IL, MA, ME, MN, NH, NY, RI, VT, WI,
Noridian Healthcare Solutions, LLC, Jurisdiction JE	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
Noridian Healthcare Solutions, LLC, Jurisdiction JF	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
Novitas Solutions, Inc	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX,
Palmetto GBA	AL, GA, TN NC, SC, VA, WV
DME MAC Jurisdictions	
CGS Administrators, LLC, Jurisdictions JB and JC	AL, AR, CO, FL, GA, IL, IN, KY, LA, MI, MN, MS, NM, NC, OH, OK, Puerto Rico, SC, TN, TX, VA, Virgin Island, WI, WV
Noridian Healthcare Solutions, LLC, Jurisdictions JA and JD	AK, American Soamoa, AZ, CA, CT, DE, DC, Guam, HI, ID, IA, KS, MA, MD, ME, MO, MT, ND, NE, NH, NJ, NV, NY, Northern Mariana Islands, OR, PA, RI, SD, UT, VT, WA, WY

Important Reminder

BCBSM and BCN follow CMS Medicare coverage guidance to limit coverage to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. Medicare Advantage Medical Policies list the criteria BCBSM and BCN use to decide which medical services are considered “reasonable and necessary” when Medicare coverage rules are not fully developed, or as otherwise may permitted by CMS Medicare regulations. Individual member benefit plan documents, such as the Evidence of Coverage and Annual Notice of Change, as well as applicable laws govern benefit coverage, including any inclusion, exclusion, and/or other restrictions.

Medicare Advantage Medical policies are created when permitted by CMS Medicare regulations, reviewed regularly, and may be revised periodically. BCBSM/BCN Medical Policies are proprietary and should not be copied or disseminated without the express, prior written approval of BCBSM. All providers are required to review applicable BCBSM reimbursement policies prior to claim submission and bill for covered services in accordance with those

policies. Additionally, providers contracted with BCBSM or BCN's Medicare Advantage network(s) should review the provider manual for any additional claim submission requirements. Providers not contracted with BCBSM or BCN's Medicare Advantage network may be required to submit documentation to BCBSM, BCN, or its delegated entity supporting billed claims, including but not limited to applicable medical records.

Note: U.S. Food and Drug Administration (FDA) approval for a specific indication or the issuance of a CPT code is not sufficient for a procedure to be considered medically reasonable and necessary. Similarly, the presence of a procedure/device code or payment amount for the service in the Medicare fee schedule does not necessarily indicate coverage. If a service is deemed not reasonable and necessary, to treat illness or injury for any reason (including lack of safety and efficacy because it is an experimental procedure, etc.), the procedure is considered not covered.

Disclaimer: This medical policy is not an authorization, certification, explanation of benefits, or a contract for the services, devices, or drugs that is referenced in the medical policy. Medical policies do not constitute medical advice and do not guarantee any results or outcomes or guarantee payment. The medical policy is not intended to replace independent medical judgment for the treatment of individuals. Treating physicians and health care providers are solely responsible for determining what care to provide to their patients. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another.

Pursuant to Section 1557 and Section 504, Blue Cross does not discriminate on the basis of race, color, national origin, age, disability, or sex (including sex characteristics, intersex traits; pregnancy or related conditions; sexual orientation; gender identity, and sex stereotypes). This includes our rules, benefit designs and medical policies.

BCBSM/BCN Medicare Advantage Policy History

Policy Effective Date	UM Committee Approval Date	Comments
07/17/2024	07/17/2024	Medicare Advantage policy established
08/16/2025	07/16/2025	Annual Review: UMC Review and approval extension
10/17/2025	09/17/2025	Annual Review: MA policy foundational language updated. Adoption of JUMP policy updates. CMS guidance updated.

Medical Policy



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Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. When Centers for Medicare and Medicaid (CMS) coverage rules are not fully developed, this medical policy may be used by BCBSM or BCN Medicare Advantage plans 42 CFR § 422.101 (b)(6). Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 9/1/25**
(See policy history boxes for previous effective dates)

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

Description/Background

Genetic testing of circulating tumor DNA (ctDNA) and circulating tumor cells in peripheral blood (referred to as “liquid biopsy”) potentially offers a noninvasive alternative to tissue biopsy for therapeutic decisions and prognosis for individuals with cancer. For individuals with non-small-cell lung cancer (NSCLC), detection of “driver mutations” or resistance variants is important for selecting individuals for targeted therapy. The tests discussed herein are intended for use in individuals with advanced (stage III or IV) non-small-cell lung cancer.

PREDICTIVE BIOMARKERS IN NON-SMALL-CELL LUNG CANCER

Several predictive genetic biomarkers have been identified for non-small-cell lung cancer (NSCLC). Somatic genome alterations known as “driver mutations” are usually transformative variants arising in cancer cells in genes encoding for proteins important in cell growth and survival. Randomized controlled trials have demonstrated improved efficacy, often in conjunction with decreased toxicity, of matching targeted therapies to individuals with specific driver mutations. Several such targeted therapies are approved by the Food and Drug Administration (FDA) for NSCLC. Guidelines generally suggest analysis of either the primary NSCLC tumor or of a metastasis for the presence of a set of driver mutations to select appropriate treatment.

Genetic Biomarkers With FDA-Approved Targeted Therapies

The list of targeted therapies approved for NSCLC is evolving. Currently, there are FDA-approved targeted therapies for epidermal growth factor receptor (*EGFR*) variants, anaplastic lymphoma kinase (*ALK*) translocations, *ROS1* translocations, and *BRAF* variants for NSCLC. Some companion diagnostics using tissue samples have also been FDA-approved to identify the associated driver mutations for the targeted therapies.

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, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication.. When treated with standard platinum-based chemotherapy, subjects with advanced NSCLC have a median survival of 8 to 11 months and 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.

***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.

***EGFR* Gene Variants**

Somatic variants in the TK 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 TKIs (afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all individuals who initially respond to an EGFR TKI experience disease progression. The most common of the secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20. The *EGFR* variant T790M has been associated with acquired resistance to TKI therapy. When the T790M variant is detected in tissue biopsies from subjects with suspected resistance to TKI therapy, osimertinib is recommended as second-line therapy. The use of osimertinib as a first-line therapy for subjects who have *EGFR*-sensitizing variants was approved by the FDA in 2018 on the basis of the randomized, double-blind phase 3 FLAURA trial.

***EGFR* Variant Frequency**

Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese subjects with early-stage squamous cell carcinoma (SCC). In a separate cohort of 63 Chinese subjects 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 subjects, Mitsudomi et al (2006) reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of subjects with nonadenocarcinoma histologies. Eberhard et al (2005) observed *EGFR* variants in 6.4% of subjects with SCC and Rosell et al (2009) observed *EGFR* variants in 11.5% of subjects 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 subjects.

ALK Gene

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The EML4-ALK fusion gene results from an inversion within the short arm of chromosome 2. The EML4-ALK rearrangement (“ALK-positive”) is detected in 3% to 6% of NSCLC individuals, 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. *BRAF* or *MEK* inhibition with TKIs (e.g., vemurafenib/dabrafenib or trametinib) was originally approved by FDA for treatment of unresectable or metastatic melanoma with *BRAF* V600 variants but the combination of dabrafenib and trametinib was expanded to include treatment of metastatic NSCLC in 2017. Most *BRAF* variants occur more frequently in smokers.

ROS1 Gene

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

KRAS Gene

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor resistant to therapies that target the EGFR. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers. *KRAS* variants can be detected by direct sequencing, polymerase chain reaction technologies, or next-generation sequencing. *EGFR*, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

RET Gene

RET (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase 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. *RET* inhibition with pralsetinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic *RET*-fusion-positive NSCLC. Approval was based on results from an open-label, non-randomized phase 1/2 trial in 114 subjects (NCT03037385). Among 27 treatment-naïve subjects, the ORR was 70% with 58% of responses lasting 6 months or longer in duration. Among 87 individuals previously treated with chemotherapy, the ORR was 57% with 80% of responses lasting 6 months or longer in duration. *RET* inhibition with selpercatinib was granted accelerated approval by the FDA in 2020 for the treatment of *RET* fusion-positive metastatic NSCLC and advanced or metastatic medullary thyroid cancer. Approval for NSCLC was based on results from an open-label, non-randomized phase 1/2 trial in 144 subjects (NCT03157128). Among 39 treatment-naïve subjects, the ORR was 85% with 58% of responses lasting 6 months or longer in duration. Among 105 subjects previously treated with platinum chemotherapy, the ORR was 64% with 81% of responses lasting 6 months or longer in duration.

MET Variants

C-MET, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor that is involved in cell survival and proliferation. *MET* (mesenchymal-epithelial transition) amplification is 1 of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs. *MET* amplification occurs in 2% to 4% of treatment-naïve NSCLC and *MET* and *EGFR* commutations occur in 5% to 20% of NSCLC tumors with acquired resistance to EGFR TKIs. *MET* exon 14 (*MET*ex14) skipping mutations occur in approximately 3% to 4% of adenocarcinomas and 1% to 2% of subjects with other NSCLC histologies. Higher frequencies are observed in older women who are nonsmokers. *MET*ex14 genomic alterations do not typically overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* variants. Several types of *MET*ex14 skipping mutations can occur, including mutations, base substitutions, and deletions. *MET* inhibition with capmatinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic NSCLC in individuals positive for *MET*ex14 skipping mutations based on results from an open-label, non-randomized, phase 2 trial in 97 subjects (NCT02414139). Among 28 treatment-naïve subjects, the overall response rate (ORR) was 68% with a response duration of 12.6 months. Among 69 previously treated subjects, the ORR was 41% with a response duration of 9.7 months. Individuals in this study were wild type for *EGFR* variants and negative for *ALK* rearrangements. In 2022, The FDA granted approval for the use of capmatinib in adults individuals for metastatic non-small cell lung cancer whose tumors have a mutation leading to mesenchymal-epithelial transition (*MET*) exon 14 skipping, as detected by an FDA-approved test. Efficacy was demonstrated in 160 patients with metastatic NSCLC with a mutation leading to *MET* exon 14 skipping.

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry. Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

NRG1

NRG1 gene in plasma, can be isolated using Next-Generation Sequencing (NGS) on isolated genomic DNA or RNA from plasma samples. RNA-based next-generation sequencing is the primary method for detecting *NRG1*. *NRG1* inhibition with zenocutuzumab-abco was granted accelerated approval by the FDA in 2024 for the treatment of NSCLC in individuals positive for *NRG1* mutations based on a multicenter, open-label, multicohort trial. The trial enrolled 64 adults with advanced or metastatic *NRG1* fusion-positive NSCLC...who had disease progression following standard of care treatment. Identification of positive *NRG1* gene fusion status was prospectively determined by next generation sequencing assays.

Genetic Biomarkers With Off-Label Targeted Therapies

Proposed targeted therapies may be used off-label for genetic alterations in *HER2* (trastuzumab, afatinib), *MET* (crizotinib), and *RET* (cabozantinib, vandetanib). 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. *RET* (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase growth factor.

Genetic Biomarkers Without Targeted Therapies

The most common predictive variant in North American populations is *KRAS*, occurring in 20% to 25% of NSCLC. Subjects with *KRAS* variants have shorter survival than those without *KRAS* variants, and thus *KRAS* is a prognostic marker. It also predicts a lack of TKI efficacy. Because *KRAS* variants are generally not found with other tumor biomarkers, *KRAS* testing might identify subjects who would not benefit from further molecular testing. Targeted therapies are under investigation for *KRAS*-variant NSCLC.

Treatment Selection

Tissue Biopsy as a Reference Standard

The standard for treatment selection in NSCLC is biomarker analysis of tissue samples obtained by biopsy or surgery. However, a lung biopsy is invasive with a slow turnaround time for obtaining results. Tissue biopsy may also be an imperfect reference standard due to inadequate sampling, tumor heterogeneity, or other factors.

Technologies for Detecting Circulating Tumor DNA

Cell-free DNA in blood is derived from nonmalignant and malignant cell DNA. The small DNA fragments released into the blood by tumor cells are referred to as circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the primary tumor, metastases or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process, generating larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origins. The ctDNA can be used for genomic characterization of the tumor and identification of the biomarkers of interest.

Detection of ctDNA is challenging because cell-free DNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (e.g., Sanger) are needed.

Sensitive and specific methods are available to detect ctDNA and identify single nucleotide variants, duplications, insertions, deletions, and structural variants. Examples of methods are as follows:

- Denaturing high-performance liquid chromatography involves polymerase chain reaction (PCR) followed by denaturing plus hybridization and then separation.
- Peptide nucleic acid-locked nucleic acid PCR suppresses wild-type *EGFR* followed by enrichment for mutated *EGFR*.
- Amplification refractory mutation system PCR generates different-sized PCR products based on the allele followed by separation of PCR fragments to determine the presence of variants.
- BEAMing combines emulsion PCR with magnetic beads and flow cytometry.
- Digital genomic technologies, such as droplet digital PCR, allow for enumeration of rare variants in complex mixtures of DNA.

Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants (“hotspots”) that occur in specific cancers, which can impact therapy decisions (e.g., *EGFR* and *ALK* in NSCLC); such testing can also be untargeted and may include array comparative genomic hybridization, next-generation sequencing (NGS), and whole exome and genome sequencing. Panel testing for specific genetic variants that may impact therapy decisions in many different cancers can also be performed.

Regulatory Status

U.S. Food and Drug Administration (FDA) -approved targeted treatments for the variants described above are summarized in Table 1. (Note this information is current as of April 22, 2025. FDA maintains a list of oncology drug approval notifications at <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancerhematologic-malignancies-approval-notifications?randparam=861689>.)

Table 1. Targeted Treatments for Non-Small-Cell Lung Cancer

Target	FDA-Approved Targeted Therapies
<i>EGFR</i>	Gefitinib (Iressa), Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) Afatinib (Gilotrif) Osimertinib (Tagrisso) Dacomitinib (Vizimpro) Mobocertinib (Exkivity)
<i>ALK</i>	Crizotinib (Xalkori) Ceritinib (Zykadia) Alectinib (Alecensa) Brigatinib (Alunbrig) Lorlatinib (Lorbrena) Ensartinib (Ensacove)
<i>BRAF</i>	Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist) Encorafenib (Braftovi) in combination with binimetinib (Mektovi)
<i>ROS1</i>	Crizotinib (Xalkori)
<i>KRAS</i>	Sotorasib (Lumakras) Adagrasib (Krazati)
<i>RET</i>	Capmatinib (Tabrecta) Tepotinib (Tepmetko)
<i>MET</i>	Capmatinib (Tabrecta) Tepotinib (Tepmetko)
<i>NTRK</i>	Larotrectinib (Vitrakvi) Entrectinib (Rozlytrek)
<i>NRG1</i>	Zenocutuzumab-zbc0 (Bizengri)

Source: FDA (2023; [12]) *ALK*: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; *MET*: mesenchymal-epithelial transition.

Table 2 summarizes the FDA-approved targeted treatments for individuals with NSCLC along with the concurrently approved companion diagnostic tests. The information in Table 2 is current as of April 22, 2025. An up-to-date list of FDA cleared or approved companion diagnostics is available at: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>.)

A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether, for a specific patient, a particular therapeutic product's benefits outweigh any potential serious side effects or risks.

Companion diagnostics can:

- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

Table 2. Targeted Treatments for Advanced Non-Small-Cell Lung Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Adagrasib (Krazati)	Adults with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy	- Agilent Resolution ctDx FIRST assay - therascreen KRAS RGQ PCR Kit	KRAS	KRYSTAL-1 NCT03785249	2A or higher/ NSCLC Treatment
Afatinib (Gilotrif)	- First-line for patients with metastatic NSCLC whose tumors have non-resistant EGFR mutations as detected by an FDA-approved test. - Limitations of Use: Safety and efficacy not established in patients whose tumors have resistant EGFR mutations - Patients with metastatic, squamous NSCLC	2013: therascreen EGFR RGQ PCR kit (Qiagen) 2016: therascreen EGFR RGQ PCR Kit (Qiagen) 2017: FoundationOne CDx™ (Foundation Medicine) 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)	EGFR	- EGFR Mutation-Positive Metastatic NSCLC: LUX-Lung 3 NCT00949650 - Non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R^a substitutions: LUX-Lung 2 (NCT00525148), LUX-Lung 3 (NCT00949650), and LUX-Lung 6 (NCT01121393) (pooled subgroup analysis) - Previously Treated, Metastatic Squamous NSCLC:	Same as above

	progressing after platinum-based chemotherapy			LUX-Lung 8 NCT01523587	
Alectinib (Alecensa)	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	ALK	ALEX NCT02075840	Same as above
amivantamab -vmjw with carboplatin and pemetrexed	Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R	No approved companion diagnostic	epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R	MARIPOSA-2 (NCT04988295)	
Brigatinib (Alunbrig)	Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	2020: Vysis ALK Break Apart FISH Probe Kit	ALK gene rearrangements	ALTA 1L NCT02737501	Same as above
Capmatinib (Tabrecta)	Metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test.	2020: FoundationOne CDx™ 2021: FoundationOne Liquid CDx™	MET single nucleotide variants and indels that lead to MET exon 14 skipping	GEOMETRY mono-1 NCT02414139	Same as above
Ceritinib (Zykadia)	Adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	2017: FoundationOne CDx™ (Foundation Medicine) 2017: VENTANA ALK (D5F3) CDx Assay	- ALK rearrangements, - ALK protein expression	First-line: ASCEND-4 NCT01828099 Second-line: ASCEND-1, NCT01283516	Same as above

Crizotinib (Xalkori)	Adults with metastatic NSCLC whose tumors are ALK- or ROS1-positive as detected by an FDA-approved test	ALK tests: 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) 2017: FoundationOne CDx™ (Foundation Medicine) ROS tests: 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)	ALK	ALK-positive: PROFILE 1014 NCT01154140 NCT00932893 ROS1-positive: PROFILE 1001 NCT00585195	Same as above
Dacomitinib (Vizimpro)	First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitutions as detected by an FDA-approved test	2018: theascreen EGFR RGQ PCR Kit 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)	EGFR	ARCHER 1050 NCT01774721	Same as above
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test	2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ (Foundation Medicine)	BRAF V600E	Study BRF113928 NCT01336634	Same as above
Encorafenib (Braftovi) plus Binimetinib (Mektovi)	- Adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, as detected by an FDA-approved test. - Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type	2023: FoundationOne® CDx 2023: FoundationOne® Liquid CDx	BRAF V600E	PHAROS NCT03915951	Same as above

	BRAF CRC, or wild-type BRAF NSCLC.				
Entrectinib (Rozlytrek)	Adult and pediatric patients 12 years of age and older with solid tumors that: - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, - are metastatic or where surgical resection is likely to result in severe morbidity, and - have either progressed following treatment or have no satisfactory alternative therapy.	2022: FoundationOne CDx (Foundation Medicine, Inc.) 2022: FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	STARTRK-2 NCT02568267 Doebele et al (2020) STARTRK-1 NCT02097810 Drilon et al (2017) Doebele et al (2020) ALKA-372-001 Doebele et al (2020) STARTRK-NG NCT02650401 Desai et al (2022)	Same as above
Erlotinib (Generic)	- First-line and maintenance treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. - Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	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) 2020: FoundationOne® Liquid CDx 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)	EGFR	NCT00874419	Same as above
Gefitinib (Iressa)	First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or	2015: theascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit	Exon 19 deletion or exon 21 L858R ^a substitution mutation	Study 1, Study 2 (Iressa Product Label)	Same as above

	exon 21 (L858R) substitutions as detected by an FDA-approved test • Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) • 2018: cobas® EGFR Mutation Test v2 (tissue or plasma test) (Roche Diagnostics) • 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)			
Larotrectinib (Vitrakvi)	Adult and pediatric patients with solid tumors who: • have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory alternative treatments or that have progressed following treatment.	• 2020: FoundationOne CDx (Foundation Medicine, Inc.) • 2024: TruSight Oncology Comprehensive (Illumina, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	Hong et al (2020), - Pooled analysis of 3 studies: • LOXO-TRK-14001 NCT02122913 • SCOUT NCT02637687 NAVIGATE NCT02576431	Same as above
Lazertinib (Lazcluze)	• Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with	• 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics)	EGFR exon 19 deletions or exon 21 (L858R) substitution mutations	Mariposa NCT04487080	Same as above

	epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test				
Lorlatinib (Lorbrena)	Adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	2021: Ventana ALK (D5F3) CDx Assay	ALK	CROWN NCT03052608	Same as above
Mobocertinib (Exkivity)	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: Oncomine Dx Target Test	EGFR	EXCLAIM NCT02716116	Same as above
Osimertinib (Tagrisso)	- Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. - First-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as	2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma)^a 2017-2019: FoundationOne CDx™ (Foundation Medicine) 2020: Guardant360 CDx 2020: FoundationOne® Liquid CDx	EGFR	- Monotherapy treatment AURA Ext NCT01802632; AURA2 NCT02094261 - Adjuvant treatment: ADAURA NCT02511106 - Disease has not progressed during/following platinum based chemoradiation therapy. LAURA trial NCT03521154 - Adjuvant treatment: FLAURA2 NCT04035486 - First-line, EGFR - Positive Metastatic NSCLC: FLAURA NCT02296125 - Previously Treated EGFR T790M	Same as above

	detected by an FDA-approved test. Treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.			Mutation-Positive: AURA3	
Pralsetinib (Gavreto)	Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	2020: Oncomine Dx Target Test	RET	ARROW NCT03037385	Same as above
Selpercatinib (Retevmo)	Adult patients with metastatic RET fusion-positive NSCLC	2022: Oncomine Dx Target Test 2024: TruSight Oncology Comprehensive (Illumina, Inc.)	RET	LIBRETTO-001 NCT03157128	Same as above
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	KRAS	CodeBreak 100 NCT03600883	Same as above
Tepotinib (Tepmetko)	Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	No approved companion diagnostic	MET exon 14 skipping alterations	VISION NCT02864992	Same as above
Zenocutuzumab-zbco (Bizengri)	Adults with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene	No approved companion diagnostic	NRG1 fusion	Subsequent therapy; eNRGy Study NCT02912949	Same as above

fusion with
disease
progression on
or after prior
systemic
therapy.

^aThe Food and Drug Administration approval for the cobas EGFR Mutation Test v2 states that individuals 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. However, the plasma test may also be appropriate for individuals who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, cannot undergo biopsy, or have indeterminate histology (in whom an adenocarcinoma component cannot be excluded).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

Clinical laboratories accredited through the College of American Pathologists enroll in proficiency testing programs to measure the accuracy of the test results. There are currently no College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA laboratory-developed tests.

Agilent Resolution Bio ctDx Lung™ includes SNV/Indel, Fusions, and CNV genes with driver mutations targeted by a specific FDA-approved therapy or therapies which are currently in clinical trials. By design, the panel does not include genes that are not implicated in lung cancer. This test is NOT APPROVED by the FDA. The test is intended as a companion diagnostic to identify individuals with non-small cell lung cancer (NSCLC) who may benefit from treatment with the targeted therapy Krazati™ (adagrasib) for the *KRAS* G12C biomarker. Additionally, the test is intended to provide tumor mutation profiling for SNVs and deletions in the *EGFR* gene.

Agilent Resolution ctDx FIRST is a companion diagnostic (CDx) to identify advanced non-small cell lung cancer (NSCLC) patients with *KRAS*G12C-mutation who may benefit from treatment with KRAZATI™. KRAZATI (adagrasib) when they have received at least 1 prior systemic therapy. The ctDx FIRST test report* includes comprehensive genomic profiling on 109 genes across four types of alterations: single nucleotide variants, indels, copy number amplifications, and fusions. FDA approved in 2022. P210040.

Biocept offers (Target Selector NGS Lung Panel) blood-based assays that target variants found in non-small cell lung cancers. The test uses a proprietary real-time quantitative PCR and, using Sanger sequencing, sequences the amplified product to confirm variants. This test is NOT APPROVED by the FDA.

Biodesix's GeneStrat® and GeneStrat NGS® uses droplet digital PCR to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC. Biodesix also offers the VeriStrat® Test, a novel test to help guide treatment of immunotherapy. The Nodify XL2 Test is FDA approved (2021). However, based on a report, the test is flawed.

Circulogene Theranostics' liquid biopsy test uses a finger stick blood sample and NGS to monitor 3000 known tumor variants in 50 cancer associated genes for targeted therapy. The

test uses a proprietary method to recover necrotic and apoptotic cell death-associated cell-free DNA. This test is NOT FDA approved.

Cobas EGFR mutation test is a real-time PCR test that identifies 42 mutations in exons 18, 19, 20 and 21 of the epidermal growth factor receptor (EGFR) gene, including the T790M resistance mutation. Individuals positive by cobas EGFR Mutation Test v2 using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are candidates for treatment with Tarceva (erlotinib). Individuals who are negative by this test should undergo routine biopsy and testing for EGFR mutations with the FFPE tissue sample type.

Foundation Medicine's FoundationACT™ is a blood-based circulating tumor DNA (ctDNA) assay that provides patients and oncologists with an option for comprehensive genomic profiling when a tissue biopsy is not feasible or when tissue is not available. Hybrid capture based NGS are used to detect variants across 62 genes and fusions across 6 genes for targeted therapy in metastatic cancer. This test is not FDA approved.

FoundationOne Liquid CDx™ is clinically and analytically validated to analyze over 300 genes. Originally FDA approved in 2020 for multiple indications including *EGFR* activating mutations (Exon 19 deletions and L858R substitution mutation) in subjects with advanced and metastatic non-small cell lung cancer (NSCLC) who may benefit from treatment with IRESSA® (gefitinib), TAGRISSO® (osimertinib), and TARCEVA® (erlotinib). In 2023 the FDA expanded the indications to include people with non-small cell lung cancer who have an EGFR exon 20 insertion in their tumor DNA. Identifying whether an individual has this insertion may help people with non-small cell lung cancer get personalized treatment with EXKIVITY (mobocertinib). In Oct 2023 an FDA approval expanded the indications for use of the FoundationOne Liquid CDx to include testing people with non-small cell lung cancer who may have a specific genetic mutation called BRAF V600E in their tumors. Identifying whether a person with non-small cell lung cancer has BRAF V600E may help determine if they will benefit from treatment with BRAFTOVI (encorafenib) in combination with MEKTOVI (binimetinib).

Guardant360® CDx is a qualitative next generation sequencing-based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in 2 genes, and fusions in 4 genes.

Lucence Healthcare, Inc LiquidHallmark® analyzes circulating tumor DNA (ctDNA) in plasma using next-generation sequencing (NGS) to detect mutations in 77 genes, identify 8 gene fusions, and assess microsatellite instability and tumor mutation burden. This test is NOT APPROVED by the FDA.

Oncomine™ Dx Target Test (Thermo Fisher Scientific) is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs), insertions, and deletions in 23 genes from DNA and fusions in *ROS1* and in *RET* from RNA isolated from formalin fixed, paraffin-embedded (FFPE) tumor samples from individuals with non-small cell lung cancer (NSCLC). The test is indicated as a companion diagnostic to aid in selecting treatment with the targeted therapies for *BRAF* V600E mutation (Tafinlar [dabrafenib] in combination with Mekinist [trametinib]), *EGFR* L858R and exon 19 deletions (Iressa [gefitinib]), *EGFR* exon 20 insertions (Exkivity [mobocertinib] and Rybrent

[amivantamab-vmjw]), *RET* fusions (Gavreto [pralsetinib]), and *ROS1* fusions {Xalkori [crizotinib]}).

Sysmex OncoBEAM™ offers liquid biopsies using BEAMing technology to detect variants in *EGFR*, *KRAS*, and *BRAF* for NSCLC as well as liquid biopsies for breast, melanoma, and colorectal cancer. This test is NOT FDA approved.

Medical Policy Statement

The effectiveness and clinical utility of circulating tumor DNA of individual genes, listed multiple gene panels when more than 5 genes are tested, and FDA approved companion diagnostic tests for the management of non-small-cell lung cancer (liquid biopsy) have been established. They may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

Analyzing cell-free/circulating tumor DNA (ctDNA) alterations in the *ALK*, *EGFR*, *BRAF V600E*, *KRAS*, *ROS1*, *NTRK*, *MET exon14 skipping*, *PD-L1*, *ERBB2 (HER-2)*, and *RET* gene using **ONE** of the following methods:

- Individual genes
- Targeted multi-gene panels
- FDA approved companion diagnostic tests (e.g. Cobas® EGFR [Epidermal Growth Factor Receptor] Mutation Test v.2, FoundationOne® Liquid CDx, Guardant360® CDx)

when **ALL** of the following apply:

- Advanced stage III or IV non-small-cell lung cancer
- Clinical circumstances reflect **ONE** of the following:
 - Patient is medically unfit for invasive tissue sampling, **OR**
 - Following pathologic (biopsy) confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis and follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified
- Used to detect ctDNA for targeted therapy benefit **or** to identify patients who will not benefit from further molecular testing

Exclusions:

- Use of circulating tumor DNA (ctDNA) for any indications not mentioned above.
- Cell-free testing when the patient already meets criteria for treatment based on known biomarker status (e.g., patient has already had testing or testing is not required).

CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)

Established codes:

81191	81192	81193	81194	81210	81235
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81275	81276	81401	81404	81405	81406
81445	81455	81479	88346	88350	0239U
0242U	0326U				

Other codes (investigational, not medically necessary, etc.):

0179U	0530U
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PLA codes are considered investigational/experimental until the laboratory test the code represents is formally documented as Established in an Interim Medical Policy or Joint Uniform Medical Policy document.

Covered CPT codes may be used to represent and reimburse testing for incremental codes or multi-target codes.

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

Selecting Targeted Therapy

Potential Beneficial Outcomes

For individuals who can undergo tissue biopsy, the beneficial outcomes of a true-positive liquid biopsy result are avoidance of tissue biopsy and its associated complications. In the National Lung Screening Trial (2011), which enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers, the percentage of individuals having at least 1 complication following a diagnostic needle biopsy was approximately 11%.

For individuals 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

The harmful outcome of a false-positive liquid biopsy result is incorrect treatment with a targeted therapy instead of immunotherapy and/or chemotherapy.

Several clinical validity studies comparing liquid biopsy with tissue biopsy in patients who had advanced NSCLC for marketed tests have been published. Characteristics of the studies are shown in Table 3. Most have included testing for *EGFR* variants but a few included testing for less prevalent variants as well.

Table 3. Characteristics of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard

Study	Study Population	Design	Variants Included ^a	Timing of Reference and Index Tests
Multiple tests				
Papadimitrakopoulou et al (2020) (AURA3)	Patients harboring T790M mutation with locally advanced or metastatic NSCLC who had progressed on EGFR TKI therapy enrolled in AURA3 studies in U.S., Mexico, Canada,, Europe, Asia, and Australia	Retrospective	<i>EGFR</i>	Both tissue and blood samples collected at screening
Cobas EGFR test				
Jenkins et al (2017)	Patients with advanced NSCLC who had progressed on EGFR TKI therapy enrolled in AURA extension or AURA2 studies in U.S., Europe, Asia, and Australia	Retrospective	<i>EGFR</i> resistance	Both tissue and blood samples collected at screening/baseline
FDA SSED cobas (2016)	Patients with stage IIIB/IV NSCLC enrolled in a phase 3 RCT in Asia between 2011 and 2012	Retrospective	<i>EGFR</i>	Both tissue and blood samples collected at screening
Karlovich et al (2016)	Patients with newly diagnosed or relapsed patients with advanced (stage IIIB, IV) NSCLC in U.S., Europe, and Australia between 2011 and 2013	Prospective	<i>EGFR, BRAF</i>	Plasma was collected within 60 d of tumor biopsy
Thress et al (2015)	Patients with NSCLC enrolled in a multinational (including U.S.) phase 1 study who had progressed on an EGFR TKI therapy	Prospective	<i>EGFR</i>	Blood and tissue collected after progression and before next-line treatment; time between not specified
Mok et al (2015)	Patients enrolled in a phase 3 RCT in Asian with stage IIIB/IV NSCLC	Prospective	<i>EGFR</i>	Tissue samples from diagnosis or resection or biopsy 14 d before first study dose. Blood collected within 7 d prior to first study dose
Weber et al (2014)	Patients in Denmark with NSCLC (84% stage IV) from 2008 to 2011	Retrospective	<i>EGFR</i>	Blood samples collected a median of 10.5 mo after diagnostic biopsy
Guardant360 CDx				
FDA SSED (2020)	Patients with advanced and metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations confirmed by the cobas	Retrospective	<i>EGFR</i>	Unclear

	EGFR Mutation Test enrolled in the FLAURA phase 3 study assessing the efficacy of osimertinib vs standard EGFR TKI therapy; patients enrolled in the NILE study were used to estimate the prevalence of CDx-positive, tissue-negative patients as no plasma from FLAURA tissue-negative patients was available			
Leighl et al (2019)	Patients with biopsy-proven, previously untreated, nonsquamous NSCLC (stage IIIB/IV) enrolled in the NILE study (Non-invasive versus Invasive Lung Evaluation at 1 of 28 North American centers between 2016 and 2018)	Prospective	<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i> , <i>MET</i> , <i>RET</i>	Unclear
Schwaederle et al (2017)	Patients with lung adenocarcinoma (86% with metastatic disease) from academic medical center in California between 2014 and 2015	Retrospective, consecutive	<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i>	Median time was 0.8 mo, range not given
Thompson et al (2016)	Patients with NSCLC or suspected NSCLC (96% stage IV) from Pennsylvania between 2015 and 2016	Prospective, consecutive	<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i>	Time between tissue and blood collection ranged from 0 d to >2 y
Villaflor et al (2016)	Patients in Chicago with NSCLC (68% stage IV) who had undergone at least 1 ctDNA test at a single commercial ctDNA laboratory in 2014 and 2015	Retrospective, selection unclear	<i>EGFR</i> , <i>ROS1</i> , <i>BRAF</i>	Time between biopsy and blood draw ranged from 0 d to 7 y (median, 1.4 y)
OncoBEAM				
Ramalingam et al (2018)	Patients with locally advanced or metastatic NSCLC from the AURA study conducted in U.S., Europe, and Asia	Prospective	<i>EGFR</i>	Plasma was collected at baseline, time of tissue sample not specified
Karlovich et al (2016)	Patients with newly diagnosed or relapsed patients with advanced (stage IIIB, IV) NSCLC in U.S., Europe, and Australia between 2011 and 2013	Prospective	<i>EGFR</i> , <i>BRAF</i>	Plasma was collected within 60 d of tumor biopsy
Thress et al (2015)	Patients with NSCLC enrolled in a multinational (including U.S.) phase 1 study who had	Prospective	<i>EGFR</i>	Blood and tissue collected after progression and before next-line

	progressed on an EGFR TKI therapy			treatment; time between not specified
Biodesix ddPCR				
Mellert et al (2017)	Patients in the test utilization data had lung cancer; unclear whether the samples in the clinical validity data were from patients with advanced NSCLC, patient characteristics are not described	Retrospective and prospective, selection unclear	<i>EGFR</i> , <i>ALK</i>	Timing not described
ctDx-Lung				
Paweletz et al (2016)	Patients in Boston with advanced NSCLC with a known tumor genotype, either untreated or progressive on therapy	Prospective	<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i>	Timing not described
InVision				
Pritchett et al (2019)	Patients with untreated, advanced NSCLC; primarily from cohorts enrolled in 2 prospective US studies with 41 centers	Prospective	<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i> , <i>MET</i>	Blood collected within 12 weeks of tissue biopsy and no therapy between tissue and blood samples
Remon et al (2019)	Patients with advanced NSCLC enrolled in single-center, prospective observational study in France. Patients were either treatment naïve for advanced disease or who had tissue-based molecular profile that failed or was not performed on the primary tissue sample (treated rescue cohort)	Prospective	<i>EGFR</i> , <i>BRAF</i> , <i>MET</i>	Time between tissue biopsy and blood collection less than 100 days; median time between tissue biopsy and liquid biopsy collection was 34 days
FoundationOne Liquid CDx				
FDA SSED (2020)	Patients with NSCLC previously tested for EGFR mutations by the approved cobas EGFR Mutation Test v2 from unrelated clinical trials	Retrospective	<i>EGFR</i> ,	Timing not described; cobas plasma-based test results were used as the reference standard; no direct comparison to tissue

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; ctDNA: circulating tumor DNA; EGFR: epidermal growth factor receptor; FDA:U.S. Food and Drug Administration; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial; SSED: Summary of Safety and Effectiveness Data; TKI: tyrosine kinase inhibitor.

^a Noting *EGFR*, *ALK*, *ROS1*, *MET*, *RET*, and *BRAF* variants only.

Table 4 summarizes the results of clinical validity 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 positive percent agreement and negative percent agreement, 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 detection of *EGFR*-resistance variants, fewer studies are available and estimates of specificity are more variable. For detection of less prevalent driver mutations, such as *ALK* and *ROS1* translocations and *BRAFV600E*, *RET* fusions, and *MET* exon 14 skipping, few publications are available and, in these publications, only a very few variants have been identified.

Table 4. Results of Clinical Validity Studies of Liquid Biopsy With Tissue Biopsy as the Reference Standard

Study	Initial N	Final N	Excluded Samples	Sensitivity (95% CI)	Specificity (95% CI)
COBAS EGFR TEST					
<i>Papadimitrakopoulou et al (2020) (AURA3)</i>	562		No plasma sample; mainland China patients; withdrawn informed consent; invalid tests		
• <i>EGFR</i> exon 19 deletion (sensitizing)		216		84 (78 to 90)	99 (92 to 100)
• <i>EGFR</i> exon 21 substitution (L858R, sensitizing)		216		60 (47 to 72)	100 (98 to 100)
• <i>EGFR</i> exon 20 (T790M, resistance)		215		51 (44 to 58)	NA ^d
Jenkins et al (2017)					
• <i>EGFR</i> exon 19 deletion (sensitizing)	710	551	No plasma sample	85 (81 to 89)	98 (95 to 100)
• <i>EGFR</i> exon 21 substitution (L858R, sensitizing)				76 (69 to 82)	98 (96 to 99)
• <i>EGFR</i> exon 20 (T790M, resistance)	710	551		61 (57 to 66)	79 (70 to 85)
FDA SSED cobas (2016)					
• <i>EGFR</i> -sensitizing variants	601	431	Insufficient plasma; invalid test result	77 (71 to 82)	98 (95 to 99)
Karlovich et al (2016)					
• <i>EGFR</i> -sensitizing variants	174	110	No matching tumor and plasma or inadequate tissue	73 (62 to 83)	100 (86 to 100)
• <i>EGFR</i> exon 20 (T790M, resistance)	174	110		64 (45 to 80)	98 (91 to 100)

Thress et al (2015)					
• EGFR exon 19 deletion (sensitizing)	NR	72	Inadequate tumor tissue	82 (63 to 94)	97 (83 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)	NR	72		87 (66 to 97)	97 (85 to 100)
• EGFR exon 20 (T790M, resistance)	NR	72		73 (57 to 86)	67 (45 to 84)
Mok et al (2015)					
• EGFR-sensitizing variants	397	238	Insufficient plasma or tissue; invalid test result	75 (65 to 83)	96 (92 to 99)
Weber et al (2014)					
• EGFR-sensitizing and - resistance variants	199 ^a	196	Inadequate tumor tissue	61 (41 to 78)	96 (92 to 99)
GUARDANT360 CDX					
• FDA SSED (2020)					
• EGFR-sensitizing variants; FLAURA	556	380	No pretreatment plasma; invalid test result; informed consent withdrawn; China mainland patient	75 (70 to 79)	NR ^d
• EGFR exon 19 deletion (sensitizing)		380		78 (72 to 83)	99 (96 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)		380		71 (62 to 78)	99 (97 to 100)
• EGFR-sensitizing variants; NILE	92	88	No pretreatment plasma or tissue; informed consent withdrawn; invalid test result	100 (77 to 100)	99 (93 to 100)
Papadimitrakopoulou et al (2020) (AURA3)					
	562		No plasma sample; mainland China patients; withdrawn informed consent; invalid tests		
• EGFR exon 19 deletion (sensitizing)		208		79 (72 to 86)	99 (92 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)		208		63 (50 to 74)	100 (98 to 100)

• <i>EGFR</i> exon 20 (T790M, resistance)	207	51 (44 to 58) 66 (59 to 72)	66 (59 to 72)	NA ^d	
Leighl et al (2019)	307	No pretreatment ctDNA (4); no tissue genotyping (4); received prohibited treatment (8); metastatic disease not confirmed (4); squamous cell (5)			
• <i>EGFR</i> exon 19 deletion (sensitizing)	223		81 (60 to 95) ^c	100 (98 to 100) ^c	
• <i>EGFR</i> exon 21 substitution (L858R, sensitizing)	223		90 (56 to 100) ^c	100 (98 to 100) ^c	
• <i>ALK</i> fusion	215		63 (24 to 91) ^c	100 (98 to 100) ^c	
• <i>ROS1</i> fusion	153		0 (0 to 84) ^c	100 (98 to 100) ^c	
• <i>BRAF</i> V600E	92		100 (16 to 100) ^c	100 (96 to 100) ^c	
• <i>MET</i> exon 14 skipping	57		80 (30 to 99) ^c	98 (88 to 100) ^c	
• <i>RET</i> fusion	57		None identified	None identified	
Schwaederle et al (2017)					
• <i>EGFR</i> variants (various)	88	34	No tissue	54 (25 to 81)	90 (70 to 99)
Thompson et al (2016)	102	50	Insufficient tissue		
• <i>EGFR</i> -sensitizing				79 (58 to 93) ^c	100 (87 to 100) ^c
• <i>EGFR</i> -resistance				50 (7 to 93) ^c	87 (74 to 95) ^c
• <i>ALK</i> fusion				None identified	None identified
• <i>ROS1</i> fusion				None identified	None identified
• <i>BRAF</i> V600E				100 (2.5 to 100) ^c	100 (93 to 100) ^c
Villaflor et al (2016)	68	31	No tissue		
• <i>EGFR</i> -sensitizing				63 (24 to 91) ^c	96 (78 to 100) ^c
• <i>ROS1</i>				None identified	None identified
• <i>BRAF</i> V600E				None identified	None identified
ONCOBEAM					

Ramalingam et al (2018)	60	51	Tissue or plasma not available		
• EGFR exon 19 deletion (sensitizing)				82 (60 to 95)	100 (88 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)				63 (41 to 81)	96 (81 to 100)
• EGFR exon 20 (T790M, resistance)				100 (40 to 100)	98 (89 to 100)
Karlovich et al (2016)10					
• EGFR-sensitizing variants	174	77	No matching tumor and plasma or inadequate tissue	82 (70 to 90)	67 (9 to 99)
• EGFR exon 20 (T790M, resistance)	174	77		73 (58 to 85)	50 (26 to 74)
Thress et al (2015)					
• EGFR exon 19 deletion (sensitizing)	NR	72	Inadequate tumor tissue	82 (63 to 94)	97 (83 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)				87 (66 to 97)	97 (85 to 100)
• EGFR exon 20 (T790M, resistance)	NR	72		80 (65 to 91)	58 (36 to 78)
BIODESIX DDPCR					
Papadimitrakopoulou et al (2020) (AURA3)	562		No plasma sample; mainland China patients; withdrawn informed consent; invalid tests		
• EGFR exon 19 deletion (sensitizing)		190		73 (64 to 80)	100 (94 to 100)
• EGFR exon 21 substitution (L858R, sensitizing)		189		70 (57 to 81)	98 (95 to 100)
• EGFR exon 20 (T790M, resistance)		189		66 (59 to 72)	NA ^d
Mellert et al (2017)					
• EGFR exon 19 deletion (sensitizing)		92		96 (NR)	100 (NR)
• EGFR exon 21 substitution (L858R, sensitizing)		73		100 (NR)	100 (NR)
• EGFR exon 20 (T790M, resistance)		55		87 (NR)	100 (NR)
• ALK fusion		24		~85 (NR)	100 (NR)
CTDX-LUNG					
Paweletz et al (2016)	NR	48	NR		
• EGFR exon 19 deletion (sensitizing)				89 (65 to 99) ^c	100 (88 to 100) ^c

• <i>EGFR</i> exon 21 substitution (L858R, sensitizing)			67 (9 to 99) ^c	100 (92 to 100) ^c
• <i>ALK</i> fusion			67 (9 to 99) ^c	100 (92 to 100) ^c
• <i>ROS1</i> fusion			100 (16 to 100) ^c	100 (92 to 100) ^c
• <i>BRAF</i> V600E			0 (0 to 98) ^c	100 (92 to 100) ^c
INVISION				
<i>Pritchett et al (2019)</i>	264	Missing tissue or ctDNA testing		
• <i>EGFR</i> exons 18-21	114		100 (75 to 100) ^{b,c}	100 (96 to 100) ^{b,c}
• <i>ALK/ROS1</i> fusions	234		40 (5 to 85) ^{b,c}	100 (98 to 100) ^{b,c}
• <i>BRAF</i> V600E	109		100 (48 to 100) ^{b,c}	100 (97 to 100) ^{b,c}
• <i>MET</i> exon 14 skipping	139		50 (14 to 86) ^{b,c}	100 (97 to 100) ^{b,c}
<i>Remon et al (2019)</i>	156	Missing tissue or ctDNA testing		
• <i>EGFR</i> exons 18-21	78		88 (47 to 100)	98 (91 to 100)
• <i>BRAF</i> V600E	75		50 (1 to 100)	100 (95 to 100)
• <i>MET</i> exon 14 skipping	48		33 (2 to 87)	100 (90 to 100)
FOUNDATIONONE LIQUID CDX				
<i>FDA SSED (2020)</i>	280	Samples in which there was insufficient plasma to process both replicates of the cobas reference test		
• <i>EGFR</i> exon 19 deletion (sensitizing)	135		95 (83 to 99) ^c (rep 1) 95 (83 to 99) ^c (rep 2)	96 (89 to 99) ^c (rep 1) 96 (89 to 99) ^c (rep 2)
• <i>EGFR</i> exon 21 substitution (L858R, sensitizing)	133		95 (83 to 99) ^c (rep 1) 100 (89 to 100) ^c (rep 2)	96 (89 to 99) ^c (rep 1) 94 (86 to 97) ^c (rep 2)
• <i>EGFR</i> -sensitizing (combined)	177		98 (91 to 100) ^c (rep 1) 98	96 (89 to 99) ^c (rep 1) 93

	(91 to 100) ^c (rep 2)	(85 to 97) ^c (rep 2)
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CI: confidence interval; ctDNA: circulating tumor DNA; *EGFR*: epidermal growth factor receptor; FDA: Food and Drug Administration; NR: not reported; SSED: Summary of Safety and Effectiveness Data.

^a Unclear how many samples were eligible but not included

^c Not reported; calculated based on data provided

^d Not applicable; cannot calculate due to lack of mutation negative samples

^e Compared to Roche cobas EGFR Mutation Test v2

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, or OncoBEAM tests), can support its utility for the purpose of selecting treatment with *EGFR* TKIs (i.e., erlotinib, gefitinib, afatinib). A robust body of evidence (see Table 4) has demonstrated moderate sensitivity (> 63%) with high specificities (>95%) for these 3 tests. If 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 individuals 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 (eg, cobas), 86% of the individuals would then require tissue testing to detect the remaining individuals 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 individuals would be subject to repeat testing. There is extremely limited evidence on whether the “false-positives” (i.e., subjects with positive liquid biopsy and negative tissue biopsy) might have been incorrectly identified as negative on tissue biopsy. In 1 study, 3 subjects with negative tissue biopsies and positive liquid biopsies appeared to respond to *EGFR* TKI inhibitors.

Testing for *EGFR* Variants with Circulating Tumor DNA (Liquid Biopsy)

Tests which have multiple studies of adequate quality to estimate the performance characteristics for *EGFR* TKI-sensitizing variants with sufficient precision include the cobas, Guardant360, and OncoBEAM.

For individuals with advanced-stage NSCLC who receive somatic testing for *EGFR* variants or ALK rearrangements using circulating tumor DNA (ctDNA) (liquid biopsy) to guide targeted treatment with TKIs, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher.

Lee et al (2014) designed a meta-analysis of randomized controlled trials (RCTs) of *EGFR* TKIs vs chemotherapy in individuals without *EGFR*-sensitizing variants, the overall median progression-free survival (PFS) was 6.4 months in subjects assigned to chemotherapy vs 1.9 months in subjects 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 subjects without *EGFR*-sensitizing variants was true in both the first- and second-line setting.

The FDA SSED (2020) document supporting the approval of Guardant360 CDx reported clinical outcome data derived from the FLAURA study, a randomized phase 3 trial of osimertinib vs gefitinib or erlotinib in the first-line treatment of individuals with locally advanced and metastatic NSCLC. Subjects with *EGFR* variants detected from tissue biopsies were enrolled (n=556). A subset of plasma pretreatment samples were tested with an earlier test version, Guardant360 LDT, as part of an exploratory analysis of individuals 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 subjects. Samples from 27 subjects 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 vs LDT discordance; these imputed results did not significantly deviate from the original observations (HR=0.40-0.42). The SSED document also provided a concordance analysis between Guardant360 CDx and Guardant360 LDT test versions in NSCLC subjects 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.

The FDA SSED document (2016) supporting the approval of the cobas *EGFR* Mutation Test v2, reported clinical outcome data derived from a randomized phase 3 trial of erlotinib vs gemcitabine plus cisplatin as first-line treatment of NSCLC. However, only subjects 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 subjects with a sensitizing *EGFR* variant. Among the subset of subjects 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.

Oxnard et al (2016) compared outcomes by T790M status for liquid biopsy and tissue biopsy in subjects enrolled in the escalation and expansion cohorts of the phase 1 AURA study of osimertinib for advanced *EGFR*-variant NSCLC. Some subjects may have overlapped with the Thress study (2015). 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=.001), as was median PFS (16.5 months vs 2.8 months; p=.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=.004; PFS=4.2 months; p=.0002) which is consistent with false-positive ctDNA results. The authors concluded that a T790-variant ctDNA assay could be used for osimertinib treatment decisions in individuals with acquired *EGFR* TKI resistance and would permit avoiding tissue biopsy for patients with T790M-positive ctDNA results.

Papadimitrakopoulou et al (2020) compared outcomes in tissue-positive T790M subjects 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. 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, individuals 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.

In the AURA3 trial, subjects with liquid-positive tests were associated with increased disease burden and increased plasma test sensitivity compared to liquid-negative subjects. 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 American Society of Clinical Oncology with an expert consensus opinion that "Physicians may use plasma cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma subjects 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.

Section Summary: Clinical Valid

The cobas test has very high accuracy (area under the receiver operating characteristic curve [AUROC], 0.96), a sensitivity of about 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 United States, primarily in individuals with advanced disease of adenocarcinoma histology. The Guardant360 CDx test has 5 studies using tissue biopsy as the reference standard performed in the United States in the intended-use population for *EGFR* TKI-sensitizing variants. Estimates of specificity are consistently 90% or higher. Likewise, the OncoBEAM test has 3 studies using tissue biopsy in Asia, Europe, Australia, and the United States in the intended-use population, 2 of which provide precise estimates for specificity that are very high (>95%)

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 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.

Other Variants with Circulating Tumor DNA (Liquid Biopsy)

For tests other than the cobas test, Guardant360 CDx, and OncoBEAM 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. However, this study does not meet selection criteria due to use of a non-tissue comparator and non-inferiority margins were not described in the FDA summary.

Few studies have examined the performance of liquid biopsy for 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.

Per National Comprehensive Cancer Network Guidelines *EGFR*, *KRAS*, *ROS1* and *ALK* genetic alterations do not usually overlap, thus testing for *KRAS* mutations may identify individuals who will not benefit from further molecular testing. Targeted therapy is not currently available for individuals with *KRAS* mutations. *KRAS* mutation is prognostic of poor survival for patients with NSCLC. *KRAS* mutations are also predictive of a lack of benefit from *EGFR* tyrosine Kinase Inhibitor (TKI) therapy.

Section Summary: Clinically Useful

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, or OncoBEAM, can support the clinical utility of these tests. The body of evidence has demonstrated moderate sensitivity (>63%), with high specificities (>96%). If 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 individuals with *EGFR* TKI-sensitizing variants.

Summary of Evidence

Per National Comprehensive Cancer Network Guidelines, testing for *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, *ERBB2 (HER2)*, and *NRG1* are predictive biomarkers that are helpful in determining the benefit/lack thereof of targeted therapy (category 2A).

For individuals with NSCLC who receive testing for biomarkers of *EGFR* TKIs sensitivity using target testing or proprietary ctDNA panels (cobas *EGFR* Mutation Test v2, Guardant360 CDx, and OncoBEAM tests) the evidence includes FDA approved therapeutics with NCCN recommendations of 2A or higher, a meta-analysis, and multiple randomized controlled trials. For individuals who may benefit from targeted therapy *EGFR*, *ROS1*, *ALK*, *BRAF*, *NRG1*, and *NTRK* are helpful in determining the best course of therapy. *KRAS* mutation is prognostic of poor survival as a targeted therapy is not currently available. The genetic alterations with *EGFR*, *ROS1*, *ALK*, and *KRAS* do not usually overlap, thus *KRAS* testing may identify individuals who will not benefit from further molecular testing. *KRAS* mutations are also predictive of a lack of benefit from *EGFR* tyrosine Kinase Inhibitor (TKI) therapy. The NCCN supports complete genotyping for *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, , *NRG1*, *MET*, and *RET* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable.] Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation.

The cobas *EGFR* Mutation Test has adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. The 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 individuals with *EGFR* TKI-sensitizing variants. Individuals who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. The cobas test can identify individuals for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The Guardant360 CDx and OncoBEAM 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. Evidence indicates that the reflex testing strategy with the Guardant360 CDx or OncoBEAM tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of individuals with *EGFR* TKI-sensitizing variants. Individuals who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify individuals for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with tests other than the cobas *EGFR* Mutation Test v2, Guardant360 CDx, or OncoBEAM, the evidence is lacking. 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, and OncoBEAM tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. The evidence is insufficient to determine the effects of all other technologies on health outcomes.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines discuss the role of liquid biopsy in the management of non-small-cell lung cancer (NSCLC) including the following complete genotyping for *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, *ERBB2* (*HER2*), and *NRG1* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are considered acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. The guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of histologic tissue diagnosis. They also state that cfDNA testing can be used if the patient is not medically fit for invasive tissue sampling or there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified. The guidelines also state that plasma or tissue-based testing via broad molecular profiling should be considered at progression, for the T790M mutation and other genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with re-biopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

The guidelines additionally state that if there is insufficient tissue to allow testing for *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, and *RET*, repeat biopsy and/or plasma testing should be done. If not feasible, treatment should be guided by available results, and if mutation status is unknown, patients are treated as though they do not have driver oncogenes. Diagnosis of NSCLC should be guided by tissue. The guidelines do not endorse any specific commercially available test.

International Association for the Study of Lung Cancer

The International Association for the Study of Lung Cancer (Rolfó et al; 2018) published a statement paper on liquid biopsy for advanced non-small-cell lung cancer. The work preparing the statement was supported by unrestricted grants from Guardant Health, Astra Zeneca, Biocept, and Roche. The statement made the following recommendations:

- “The criteria used to select treatment-naïve patients for molecular testing of ctDNA [circulating tumor DNA] is the same used for molecular testing using DNA isolated from tissue.”
- “Liquid biopsy can be considered at the time of initial diagnosis in all patients who need tumor molecular profiling, but it is particularly recommended when tumor tissue is scarce, unavailable, or a significant delay potentially greater than 2 weeks is expected in obtaining tumor tissue.”

The following tests are acceptable to detect epidermal growth factor receptor (*EGFR*)-sensitizing variants and results are sufficient to start a first-line treatment with an *EGFR* tyrosine kinase inhibitor:

- Cobas *EGFR* Mutation Test v2.
- droplet digital polymerase chain reaction next-generation sequencing panels
- Multiplex panels using next-generation sequencing platforms could be considered to detect *EGFR*, *ALK*, *ROS1*, or *BRAF* variants and a positive result would be adequate to initiate first-line therapy.

A next-generation sequencing multiplex panel was preferred to detect T790M and other common resistance alterations. A positive result for *EGFR* T790M should be considered adequate to initiate osimertinib in the second-line setting.

In 2021 the IASLC (Roflo et al) updated their recommendations to include the following:

- Testing of plasma ctDNA should be performed by a clinically validated NGS platform rather than single-gene, PCR-based approaches, both in treatment-naïve patients and those associated with multiple mechanisms of acquired resistance (MOR) to targeted agents. Where plasma NGS is not available owing to technical and economic constraints, single-gene or low multiplex-based approaches may represent appropriate alternatives. Use of limited PCR analysis for *EGFR* mutations as the initial step in molecular assessment, for example, remains highly relevant in areas of the world where the *EGFR* mutation rate is high. Nevertheless, single-gene testing should not be considered complete, and if negative, serial testing for additional actionable biomarkers must be pursued.
- The benefit of tissue and plasma NGS is now established in several clinical practice settings. It is anticipated, owing to broad-based coverage of requisite oncogenes, decreased turnaround times, and emerging data on cost effectiveness, that in the near future, NGS will become increasingly available worldwide. Implementation of a multidisciplinary Molecular tumor board (MTB) to assist clinicians in treatment decision-making is advisable, as described previously.
- Plasma ctDNA can now be considered a valid tool for genotyping of newly diagnosed patients with advanced NSCLC, and results are often complementary to those of tissue analysis. At the time of acquired resistance after tyrosine kinase inhibitor (TKI) therapy in an oncogene-driven NSCLC, initial use of ctDNA is preferred for evaluation of mechanisms of resistance (“plasma-first”), with repeat tissue biopsy if plasma ctDNA is uninformative. Owing to ease of serial sampling and high patient acceptance, ctDNA is also emerging as the preferred method for real-time monitoring.
- In patients with oncogene addicted NSCLC, liquid biopsy is emerging as not only complementary to tissue-based analysis but also acceptable as the initial approach (“plasma first”) for biomarker evaluation at the time of diagnosis and for monitoring the efficacy of targeted therapies. Finally, a plasma-first approach is appropriate for identification of MOR to targeted therapies in many clinical settings.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 9.

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04238130	Evaluation Perioperative Dynamic Changes in ctDNA From Patients of Non-Small-Cell Lung Cancer Following Resection for Relapse Prediction (EVOLUTION)	132	Dec 2024 (completed)
NCT04178889	Second Primary Lung Cancer Cohort Study (SPORT)	850	Dec 2024 (unknown status)
NCT05198154	ctDNA Analysis to Monitor the Risk of Progression After First-line Immunotherapy in Patients With Advanced NSCLC (CR1STAL)	100	Dec 2025

NCT04585477	Adjuvant ctDNA-Adapted Personalized Treatment in Early Stage NSCLC (ADAPT-E)	80	Dec 2026
NCT06902272	CtDNA to Predict Response to Chemo-Immunotherapy and Detect Minimal Residual Disease in Non-Small Cell Lung Cancer (DNA-PREDICT)	30	June 2029

NCT: national clinical trial.

Government Regulations

National:

Next Generation Sequencing (NGS). 100-3; Section **90.2**; version 2. Effective 1/27/20

Item/Service Description

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. **NEXT GENERATION SEQUENCING (NGS)** is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test. This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for RNA sequencing and protein analysis.

Indications and Limitations of Coverage

B. Nationally Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that **NEXT GENERATION SEQUENCING (NGS)** as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

- i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
- ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
- iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:

- i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
- iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

- a. Patient has:
 - i. ovarian or breast cancer; and,
 - ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
 - iii. a risk factor for germline (inherited) breast or ovarian cancer; and
 - iv. not been previously tested with the same germline test using NGS for the same germline genetic content.
- b. The diagnostic laboratory test using NGS must have all of the following:
 - i. FDA-approval or clearance; and,
 - ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. Nationally Non-Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with acquired (somatic) cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1., above.

D. Other

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with advanced cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

- a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
- b. not been previously tested with the same test using NGS for the same cancer genetic content, and
- c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:

- a. any cancer diagnosis; and,
- b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
- c. a risk factor for germline (inherited) cancer; and,
- d. not been previously tested with the same germline test using NGS for the same germline genetic content.

(This NCD last reviewed January 2020)

Local:

LCD: MoIDX: **Minimal Residual Disease Testing for Cancer** (L38835); Original date: 12/26/21; Revision date: 10/26/23

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for minimally invasive molecular deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) tests that detect MINIMAL RESIDUAL DISEASE (MRD) in patients with a personal history of cancer.

This Contractor provides limited coverage for MRD testing in cancer when ALL of the following are true:

If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD 90.2 are fulfilled (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously tested with the same test for the same genetic content) or are not applicable (the patient does not have cancer as defined below)

The patient has a personal history of cancer, the type and staging of which is within the intended use of the MRD test

The identification of recurrence or progression of disease within the intended use population of the test is identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management.

The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological, or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard of care for monitoring a given cancer type) of recurrence or progression.

To be reasonable and necessary, it must also be medically acceptable that the test being utilized precludes other surveillance or monitoring tests intended to provide the same or similar information unless they either (a) are required to follow-up or confirm the findings of this test or (b) are medically required for further assessment and management of the patient.

If the test is to be used for monitoring a specific therapeutic response, it must demonstrate the clinical validity of its results in published literature for the explicit management or therapy indication (allowing for the use of different drugs within the same therapeutic class, so long as they are considered 'equivalent and interchangeable' for the purpose of MRD testing, as determined by national or society guidelines).

Clinical validity (CV) of any analytes (or expression profiles) measured must be established through a study published in the peer-reviewed literature for the intended use of the test in the intended population.

The test is being used (a) in a patient who is part of the population in which the test was analytically validated and (b) according to the intended use of the test.

The MRD test [(unless it is a Food and Drug Administration (FDA)-approved and established standard-of-care single-gene polymerase chain reaction (PCR)] satisfactorily completes a technical assessment (TA) that will evaluate and confirm that the analytical validity, clinical validity, and clinical utility criteria set in this policy are met to establish the test as Reasonable and Necessary.

Tests utilizing a similar methodology or evaluating a similar molecular analyte to a test for which there is a generally accepted testing standard or for which existing coverage exists must demonstrate equivalent or superior test performance (i.e., sensitivity and/or specificity) when used for the same indication in the same intended-use population.

MRD testing often requires 2 types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline (solid and/or liquid) tumor signature as defined by the test methodology. This is followed by a series of assays run on a minimally invasive specimen (i.e., liquid biopsy or bone marrow aspirate) to detect the presence or recurrence of tumor based on the measured biomarkers, expression, or other analytes over various timepoints. Other approaches are also acceptable, based on the validity established for the individual test comprising the service. This series of assays comprises a single test when the patient is known to have cancer.

LCD: MoIDX: **Plasma-Based Genomic Profiling in Solid Tumors** (L38168); Original Effective Date: 3/15/20; Revision date: 3/26/25

This is a limited coverage policy for next generation sequencing (NGS) assays performed on solid tumor cell free DNA in plasma, from here on called “liquid biopsies.”

Criteria for Coverage

Guardant360 CDx ® is covered only when **all** of the following conditions are met:

- Patient has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system. Patients who would meet all of the indications on the FDA label for larotrectinib if they are found to have an NTRK mutation may be considered to have advanced cancer, **and**
- Patient has not previously been tested with the Guardant360® test for the same primary cancer. For a patient who has been tested previously using Guardant360® for a cancer, that patient may not be tested again unless he or she has a new primary cancer diagnosis. In a patient with previously tested primary cancer, who has evidence of new malignant growth, that growth may be considered to be a different primary cancer if it does not originate from the same cell line or it is physiologically different enough that it responds differently to treatment than the previously tested cancer, **and**
- Patient is untreated for the primary cancer being tested or the patient is not responding to treatment (e.g., progression or new lesions on treatment), **and**
- The patient has decided to seek further cancer treatment with the following conditions:
 - The patient is a candidate for further treatment with a drug that is either FDA-approved for that patient’s cancer, or has an NCCN 1 or NCCN 2A recommendation for that patient’s cancer, **and**
 - The FDA-approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360® assay **and**

- Tissue-based comprehensive genomic profiling (CGP) is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) or specifically in NSCLC Tissue-based CGP has shown no actionable mutations.

If no alteration is detected by Guardant360® or if ctDNA is insufficient/not detected, tissue-based genotyping should be considered.

Other liquid biopsies will be covered for the same indications if they display similar performance in their intended use applications to Guardant360®.

LCD: MoIDX: **GUARDANT360 CDx ® Plasma-Based Comprehensive Genomic Profiling in Non-Small Cell Lung Cancer (NSCLC)** (L37671); Original effective date: 10/17/18; **RETIRED 3/14/20**

Coverage Indications, Limitations, and/or Medical Necessity

This policy provides limited coverage for **GUARDANT360 CDx ®** (**GUARDANT** Health, Redwood City, CA), a plasma-based comprehensive somatic genomic profiling test (hereafter called CGP) for patients with Stage IIIB/IV non-small cell lung cancer (NSCLC):

- **At diagnosis-Untreated Patient**
 - when results for EGFR single nucleotide variants (SNVs) and (insertions and deletions (indels)); rearrangements in ALK and ROS1; and SNVs for BRAF are not available **AND** when tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated);
- OR**
- **At progression-Treated Patient**
 - For patients progressing on or after chemotherapy or immunotherapy who have never been tested for EGFR SNVs and indels, and rearrangements in ALK and ROS1; and SNVs for BRAFs, and for whom tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP); **OR**
 - For patients progressing on any tyrosine kinase inhibitors (TKIs).

If no genetic alteration is detected by **GUARDANT360**, or if circulating tumor DNA (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

LCD: **Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer** (L37921)
Original effective date: 4/15/19; Revision date: 11/30/23

Coverage Indications, Limitations, and/or Medical Necessity

This test is a “**LIQUID BIOPSY**.” It is intended to assist physicians caring for patients who suffer from a common form of lung cancer and who have advanced disease.

This policy provides limited coverage for InvisionFirst™ - Lung (Inivata, Research Triangle Park, NC) (hereafter InVision) a plasma-based, somatic comprehensive genomic profiling test (CGP) for patients with advanced (Stage IIIB/IV) non-small cell lung cancer (NSCLC):

- **At diagnosis –**
 - When results for EGFR single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and SNVs for BRAF are not available **AND** when tissue-based CGP is infeasible [i.e., quantity not

sufficient (QNS) for tissue-based CGP or invasive biopsy is medically contraindicated],

or

- **At progression –**

- For patients progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR SNVs and indels; rearrangements in ALK and ROS1; and SNVs for BRAFs, and for whom tissue-based CGP is infeasible;

or

- For patients progressing on EGFR tyrosine kinase inhibitors (TKIs),

If no genetic alteration is detected by InVision or if circulating tumor DNA (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

Local Coverage Article: **FDA approved EGFR Tests** (A55193); Original Effective Date: 2/16/17; Revision Date: 5/30/2024

Two tests have met the FDA criteria for EGFR genetic testing:

1. Effective 6/01/16

cobas EGFR Mutation Test is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. Defined EGFR mutations are detected using DNA isolated from formalin-fixed paraffin embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anticoagulated peripheral whole blood.

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in the Table below in accordance with the approved therapeutic product labeling:

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	EXON 19 deletions and L858R	EXON 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of EGFR **EXON 19** deletions or L858R mutations are eligible for treatment with TARCEVA® (erlotinib). Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.

2. Effective 7/12/13

therascreen EGFR RGQ PCR kit for the detection of the epidermal growth factor receptor (EGFR) gene for non-small cell lung cancer (NSCLC) tumor tissue to help select patients with NSCLC for whom GILOTRIF™ (afatinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated.

LCD: **MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer.** (L39040) Original effective date: 7/3/22. Revision date: 4/18/24

Coverage Indications, Limitations, and/or Medical Necessity

This policy describes and clarifies coverage for Lab-Developed Tests (LDTs), Federal Drug Administration (FDA)-cleared, and FDA-approved clinical laboratory tests in hereditary cancer tests including Next-Generation Sequencing (NGS) tests as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage. This policy's scope is specific for hereditary germline testing, and is exclusive of polygenic risk scores, solid tumor, hematologic malignancies, circulating tumor deoxyribonucleic acid (DNA) testing (ctDNA), and other acquired cancer-related tests.

Criteria for Coverage

All the following must be present for coverage eligibility:

- The patient must have:
 - Any cancer diagnosis
 - AND a clinical indication for germline (inherited) testing for hereditary cancer
 - AND a risk factor for germline (inherited) cancer
 - AND has not been previously tested for the same germline genetic content.
- The test has satisfactorily completed a Technical Assessment (TA) by Molecular Diagnostic Services Program (MoIDX®) for the stated indications of the test.
- The test performed includes **at least** the minimum genetic content (genes or genetic variants) with definitive or well-established guidelines-based evidence required for clinical decision making for its intended use that can be reasonably detected by the test.
 - Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents, such as the MoIDX® TA forms.
 - A single gene or variant may be tested if it is the only gene or variant considered to be reasonable and necessary for a cancer type.
- If a previous test was performed with a similar/duplicative intended use, a subsequent test is only reasonable and necessary if the non-duplicative genetic content of the second test is reasonable and necessary.
- If the test is an NGS test, it must abide by all conditions listed in the NCD 90.2.

Situations in which a test should not be used, or coverage is denied:

The test in question will be non-covered if:

- It is an NGS test and does not fulfill all the criteria set forth in the NCD 90.2
- A previous test was performed for the same genetic content
- It is a panel or single gene test used to identify a known familial variant(s) that could be identified with a test targeted to that specific variant(s)
- It is a panel or single gene test used to confirm a variant(s) detected by somatic tumor testing that can be confirmed by a test targeted to that specific variant(s)
- A satisfactory TA is not completed
- For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by the original effective date of the policy or coverage will be denied.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated

Related Policies

- Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
 - Genetic Testing - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
 - Genetic Testing and Counseling
 - Genetic Testing: Microarray Testing for Cancers of Unknown Primary (CUP) Origin
 - Genetic Testing-NGS Testing of Multiple Genes (Panel) for Malignant Conditions
 - Miscellaneous Genetic and Molecular Diagnostic Tests
 - Proteomic Testing for Non-Small-Cell Lung Cancer (NSCLC), e.g., VeriStrat®
 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, AND TMB)
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 4, 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/20	8/18/20		Joint policy established
9/1/21	6/15/21		Routine maintenance. Added 81445 and 81455 as Established. Added 0179U and 0239U as E&I. No change in policy status. Added references 78-88 Added 0242U as E/I Added language under the coding section: • PLA codes are considered investigational/experimental until the laboratory test the code represents is formally documented as Established in an Interim Medical Policy or Joint Uniform Medical Policy document. • Covered CPT codes may be used to represent and reimburse testing for incremental codes <u>or</u> multi-target codes. Updated MPS – the highlighted portion is the update: • The effectiveness and clinical utility of circulating tumor DNA of individual genes and listed multiple gene panels when more than 5 genes are tested for the management of non-small-cell lung cancer (liquid biopsy) has been established. It may be considered a useful therapeutic option when indicated.
9/1/22	8/23/22		• BCBSA merged this policy with GT-Molecular analysis for targeted therapy or immunotherapy of NSCLS (Nov 2021) ○ We cover more than BCBSA (per NCCN guidelines), so policies are to remain separate (JUMP Dec 2021 discussion with review of GT-Mol anal for targeted therapy - NSCLC).

			• FDA approved companion test are covered • Follow NCCN recommendations ○ HER2 and PD-L1 covered
9/1/23	6/13/23		• Routine Maintenance • Added code 0326U (Guardant360) E/I EFD 7/1/22. • CODES 81455 and 81445 was REVISED on 1/1/23. • Vendor: N/A (ky)
9/1/24	6/11/24		• Routine maintenance • Per discussion on 5/20/24: moved code 0326U from E/I to EST. 6/2023 review 0326U was directed from CU to be EI; however, per discussion, the testing platform for Guardant is considered established for later stage solid cancer or liquid cancer. • Vendor: N/A (ky)
9/1/25	6/17/25		• Routine maintenance (slp) • Vendor: N/A • Updated per FDA approvals and NCCN updates • 0530U added as EI

Next Review Date: 2nd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CIRCULATING TUMOR DNA FOR MANAGEMENT OF NON-SMALL-CELL LUNG
CANCER (LIQUID BIOPSY)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
 - *Duplicate (back-up) equipment is not a covered benefit.*