MEDICAL POLICY	**Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (All Lines of Business except Medicare)**
Effective Date: 7/1/2022  7/1/2022 Medical Officer Date	Medical Policy Number: 194 Technology Assessment Committee Approved Date: 7/16 Medical Policy Committee Approved Date: 12/16; 9/17; 5/18; 3/19; 3/2020; 6/2020; 07/2020; 12/2020; 3/2021; 7/2021; 09/2021; 11/2021; 3/2022; 6/2022

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition

- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making

- All relevant CPT/HCPCS codes billed

POLICY CRITERIA

Notes:

- Please refer to the Pharmacy Coverage Policies for information regarding targeted therapies associated with genetic testing addressed in this policy. (See Cross References section below)
- This policy addresses cell-free DNA tests (also known as circulating tumor DNA tests or liquid biopsies) for non-small cell lung cancer.
- This policy does NOT address circulating tumor cell assays. Please see the Circulating Tumor Cell and DNA Assays for Cancer Management medical policy. (See Cross References section below)

I. Genetic testing of tumor tissue for one or any combination of the following (A.-I.) somatic genetic alterations (see definition) may be considered **medically necessary** for guidance in selecting FDA-approved targeted therapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC):

A. *ALK* gene rearrangements
B. *BRAF* V600E mutation
C. *EGFR* exon 19 deletion
D. *EGFR* T790M and/or L858R point mutations
E. *HER2* (*ERBB2*) mutations
F. *MET* high-level amplification
G. *MET* exon 14 skipping mutation
H. *RET* gene rearrangements
I. *ROS1* gene rearrangements

II. Testing for expression of the PD-L1 protein in tumor tissue may be considered **medically necessary** for guidance in selecting FDA-approved targeted therapy in patients with metastatic stage IV NSCLC.

III. Genetic testing performed with circulating tumor DNA (from blood, also known as liquid biopsy or cell-free DNA) may be considered **medically necessary** for the treatment of NSCLC (all stages) when any of the following criteria are met (A.-C.):

A. Patient is medically unfit for invasive tissue sampling; **or**

B. In the initial diagnostic setting, following pathologic confirmation of a NSCLC diagnosis, there is insufficient material for molecular analysis and follow-up tissue-based analysis is planned for patient in which an oncogenic driver is not identified; **or**
C. In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available.

IV. Genetic testing performed with circulating tumor DNA is considered **investigational and not covered** for the treatment of NSCLC when criterion III. above is not met.

V. Molecular testing is considered **investigational and not covered** for guidance in selecting targeted therapy in patients with metastatic stage IV NSCLC when the criteria (I. or II) above are not met, including, but not limited to the following (A.-C.):

A. When genetic alterations other than those identified in criterion I. are requested (e.g., *EGFR* exon 20 insertions, S768I and L861Q mutations, or mutations in the ALK, RET or ROS1 genes).
B. When a genetic test is requested for targeted therapy that is not FDA-approved for NSCLC and does not have a National Comprehensive Cancer Network (NCCN) category 1 or 2A recommendation.
C. Molecular marker testing for which there is no FDA-approved therapies (e.g., *KRAS or PIK3CA* mutations).

VI. Molecular testing is considered **investigational and not covered** for guidance in selecting targeted therapy in patients with NSCLC when the patient has been diagnosed with stage I-III NSCLC.

VII. Expanded genetic panel testing which includes genes other than those listed in criterion I. above is considered **investigational and is not covered** for guidance in selecting targeted therapy in patients with NSCLC (all stages). Examples of investigational panels include, but are not limited to, the following tests:

A. FoundationOne
B. FoundationOne CDx™
C. GeneKey
D. GeneTrails NSCLC Genotyping Panel
E. GeneTrails Comprehensive Solid Tumor Panel
F. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets™ (MSK-IMPACT™)
G. Molecular Intelligence (MI) Tumor Seek™
H. Oncomine™ Dx Target
I. PGDx elio^{TM} tissue complete (Personal Genome Diagnostics, Inc.)

VIII. Proteomic testing is considered **investigational and is not covered** for screening or guidance in selecting targeted therapy in patients with NSCLC (all stages) (e.g. VeriStrat®).

IX. Proteogenomic testing is considered **investigational and is not covered** for screening or guidance in selecting targeted therapy in patients with NSCLC (all stages), including but not limited to, the following tests (A.-C.):

A. Biodesix Lung Reflex® (which includes VeriStrat® and GeneStrat®)
B. GPS Cancer™ Test
C. Molecular Intelligence (MI) Profile™

Link to Policy Summary

POLICY GUIDELINES

Definitions

Somatic mutation: A mutation that is acquired at some time during a person's life after conception. Somatic mutations are present only in certain cells, such as cancer cells, and are not found in the germ cells.

Clinical Utility

Establishing the clinical utility of any test is a key component in determining its ultimate usefulness. Clinical utility may be established when published evidence demonstrates test results can be used to:

1. Guide treatment, management, or preventive decisions; and
2. Those decisions lead to improved primary health outcomes.

Comprehensive Testing

Numerous comprehensive panel tests are available which test for various combinations of genes and/or proteins in an attempt to guide therapy decisions. These panels may contain various types of tests including protein, transcript, gene, mutation, rearrangement, fusion, deletion, insertion, and amplification testing. Some well-designed tests include only components that have demonstrated clinical utility for metastatic NSCLC therapy. However, other tests include a broader range of components for which the clinical utility of testing is not yet established. It is not recommended that patients undergo panel testing which contains components with unknown clinical significance as test

results may lead to unnecessary interventions which is not supported by current evidence or practice standards. Therefore, the clinical utility of each components included in a test must be demonstrated in order to establish the medical necessity of the panel. This principle applies to all types of tests, including but limited to genetic tests, genomics, transcriptomics (assessing RNA) and proteomics.

CPT CODES

Note: Codes which may be billed for molecular testing addressed in this policy include, but are not limited to, the following:

All Lines of Business except Medicare	
Prior Authorization Required	
0009U	Oncology (breast cancer), *ERBB2* (*HER2*) copy number by FISH, tumor cells from formalin-fixed paraffin-embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as *ERBB2* gene amplified or non-amplified
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)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
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
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
81210	*BRAF* (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81235	*EGFR* (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	*KRAS* (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	*KRAS* (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)

81401	Molecular pathology procedure, Level 2 (eg, 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)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, 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)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, *BRAF*, CDKN2A, *EGFR*, *ERBB2*, KIT, *KRAS*, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, *BRAF*, CDKN2A, CEBPA, DNMT3A, *EGFR*, *ERBB2*, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, *KRAS*, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
No Prior Authorization Required	
88271	Molecular cytogenetics; DNA probe, each
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88291	Cytogenetics and molecular cytogenetics, interpretation and report
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, *KRAS* mutational analysis)
88366	In situ hybridization (eg, FISH), per specimen; each multiplex probe stain procedure
88367	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; initial single probe stain procedure
88368	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure
88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each multiplex probe stain procedure
88381	Microdissection (ie, sample preparation of microscopically identified target); manual
Not Covered	
0022U	Targeted genomic sequence analysis panel, cholangiocarcinoma and non-small cell lung neoplasia, DNA and RNA analysis, 1-23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
Unlisted Codes	

All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

DESCRIPTION

Background

Lung cancer is the leading cause of death in the United States, with over 234,000 new cases and 154,000 deaths estimated in 2018. Fewer than 18% of patients with lung cancer have an overall survival of greater than five years after diagnosis. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers.[1]

Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC)

Treatment of NSCLC has evolved in the past decade, largely due to the advances in understanding of the molecular abnormalities underlying cancer development and progression. For NSCLC, evaluation of specific molecular abnormalities in several genes is now routinely used to guide treatment-making decisions for the selection of first-line and second-line molecule- or mutation-specific targeted therapies. Examples of specific molecular abnormalities identified in NSCLC are described below.

In addition to testing for specific molecular abnormalities through single gene and/or single protein tests and small panel tests, several laboratories have marketed larger, more comprehensive tests, with the intention of detecting other somatic mutations. These comprehensive tests typically include large numbers of genes, genetic rearrangements, and/or proteins associated with more than one oncologic indication, thereby increasing the likelihood of detecting abnormalities not specific and of unknown significance. Furthermore, the large majority of the components in these comprehensive tests do not currently have FDA-approved therapies. Examples of comprehensive molecular tests currently being marketed and/or evaluated for NSCLC therapy guidance are described below.

A list of companion diagnostic molecular tests to detect alterations for which there are U.S. Food & Drug Administration (FDA)-approved targeted therapies for NSCLC may be found in the Regulatory Status section below.

Examples of Molecular Markers and Tests Used to Guide Targeted Therapy for NSCLC

EGFR (Epidermal Growth Factor Receptor) Gene Alterations

The *EGFR* gene encodes a tyrosine kinase receptor that is often mutated in a number of malignancies, including NSCLC.[1] The most common genetic alterations in the *EGFR* gene, which are deletions in exon 19 and point mutations in exons 20 and 21 (T790M and L858R, respectively), are associated with responsiveness several FDA-approved *EGFR* tyrosine kinase inhibitors (TKIs). There are several other alterations in the *EGFR* gene, which have been identified, such as insertions in exons 19 and 20, and point mutations (L861Q, G719X, and S68I). However, these alterations are considerably less common and their responsiveness to TKIs has not been well established. Acceptable testing methods to detect *EGFR* genetic alterations, which are approved by the FDA and recommended by the NCCN guidelines, include real-time polymerase chain reaction (RT-PCR), traditional Sanger sequencing and next generation sequencing (NGS). Testing methods NOT recommended include *EGFR* protein expression using immunohistochemistry (IHC) with mutation-specific antibodies, as this approach has not been well validated.

ALK (Anaplastic Lymphoma Kinase) Gene Rearrangements

The *ALK* gene encodes a tyrosine kinase receptor that can be rearranged in NSCLC and these rearrangements are associated with responsiveness several FDA-approved *ALK* TKIs.[1] Acceptable testing methods to detect *ALK* rearrangements (FDA-approved and NCCN recommended) include fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), NGS methodologies and RT-PCR.

ROS-1 (ROS Proto-oncogene 1) Gene Rearrangements

The *ROS1* gene encodes a tyrosine kinase receptor that can be rearranged in NSCLC and these rearrangements lead to fusions with other genes, most commonly CD74, SLC34A2, CCDC6 and FIG.[1] These rearrangements are associated with responsiveness several FDA-approved oral *ROS1* TKIs. Acceptable testing methods to detect *ROS1* rearrangements (FDA-approved and NCCN recommended) include fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), NGS methodologies and RT-PCR.

BRAF (B-Raf Proto-oncogene) Gene Mutations

The *BRAF* gene encodes a serine/threonine kinase receptor that is often mutated in a number of malignancies, including NSCLC.[1] The presence of a specific mutation in the *BRAF* gene (V600E) is associated with responsiveness to combined therapy with oral inhibitors of the *BRAF* and *MEK* genes that are FDA-approved. There are several other mutations in the *BRAF* gene that have been observed in patients with NSCLC. However, the impact of *BRAF* mutations other than V600E on therapy selection is not well understood at this time. Acceptable testing methods to detect the *BRAF* V600Emutation, which are approved by the FDA and recommended by the NCCN guidelines, include real-time polymerase chain reaction (RT-PCR), traditional Sanger sequencing and next generation sequencing (NGS). Testing methods NOT recommended include *EGFR* protein expression using immunohistochemistry (IHC) with mutation-specific antibodies, as this approach has not been well validated.

PD-L1 (Programmed Death Ligand 1) Protein Expression

PD-L1 is one of two ligands that can be present on tumor cells that bind to the PD-1 receptor on T-cells. When the PD-L1 ligand is expressed, it binds to the PD-1 receptor, inactivating the T-cell and preventing T-cell mediated cell death.[1,2] NSCLC patients that express PD-L1 on tumor cells may undergo immunotherapies that target either the PD-L1 ligand or the PD-1 receptor. Acceptable testing methods to detect PD-L1 (FDA-approved and NCCN recommended) include IHC.

KRAS (*KRAS* Proto-Oncogene) Gene Mutations

The *KRAS* gene encodes an enzyme called a G protein that activates the MAP/ERK pathway within the cell to transmit signals outside of the cell.[1] Mutations in the *KRAS* gene, most commonly at codon 12, are observed in NSCLC. *KRAS* mutations are thought to impact NSCLC by creating a constitutively active protein that signals thought the same pathway as *EGFR*. This oncogenic protein may activate the same pathway independent of *EGFR*, possibly rendering the tumor resistant to TKI therapies. As such, *KRAS* mutations are thought to be prognostic and NOT predictive of TKI therapy. Of note, there are no therapies that target *KRAS* mutations available for any malignancy, including NSCLC.

Other Genetic Alterations in NSCLC

Other driver mutations have been identified in smaller numbers of NSCLC patients, including *RET* gene rearrangements, *MET* gene amplifications and exon skipping point mutations (e.g. *MET*ex14), and *HER2* (also known as *ERBB2*) gene mutations.[1] Although there are therapies that target these genetic alterations that have been FDA-approved for use in other malignancies, they are not currently approved for patients with NSCLC. Despite this, the NCCN recommends testing of the *MET*, *RET* and *HER2* genes for driver mutations, as they believe these targeted therapies are effective in NSCLC patients.

Expanded Genetic Tests

There are a number of lab developed, CLIA-approved or FDA-approved NGS-based panel tests marketed as tools to help guide targeted therapy choices for oncologic indications. Some of these tests include therapeutic targets for several malignancies concurrently, while others are specifically marketed for NSCLC. Examples of these expanded panel tests are described below.

FoundationOne CDx™ (Foundation Medicine, Inc.)

The FoundationOne CDx™ (F1CDx) test is a comprehensive NGS-based that evaluates gene substitutions, insertions, deletions, and copy number variants (CNVs) in 324 genes, 36 gene rearrangements, microsatellite instability (MSI) and PD-L1 expression (as an optional add-on), encompassing genetic alterations identified in all types of solid tumors.[3] The test uses formalin-fixed paraffin embedded (FFPE) tumor tissue specimens and is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies, including the identification of molecular targets for nine

therapies currently approved for NSCLC patients. Although this test includes some genes with proven clinical utility for guiding targeted therapy for NSCLC (*EGFR*, *ALK*, *ROS1* and *BRAF*); it also includes genes which do not have proven clinical utility for directing treatment for any indication, including NSCLC.

Oncomine™ Dx Target (ThermoFisher)

The Oncomine Dx Target test uses NGS technology to detect sequence variations in 23 genes in DNA and RNA isolated from FFPE tissue samples from patients with NSCLC.[4] DNA is used to test for mutations in the following gene: *AKT1, ALK, BRAF, CDK4, DDR2, EGFR, ERBB2, ERBB3, FGFR2, FGFR3, HRAS, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET,* and *ROS1*. RNA is used to detect *ROS1* rearrangements. Although this test includes some genes with proven clinical utility for guiding targeted therapy for NSCLC (*EGFR*, *ALK*, *ROS1* and *BRAF*); it also includes genes which do not have proven clinical utility for directing treatment for any indication, including NSCLC.

Circulating Tumor DNA Tests

There are a number of lab developed, CLIA-approved or FDA-approved circulating tumor DNA tests (also known as cell-free DNA [cf-DNA] tests, plasma genotyping or liquid biopsy) marketed as tools to help guide targeted therapy choices for oncologic indications. Some of these tests include therapeutic targets for several malignancies concurrently, while others are specifically marketed for NSCLC. Examples of these tests are described below.

GeneStrat® (Biodesix, Inc.)

The GeneStrat® circulating tumor DNA test is marketed as a noninvasive genomic test for patients with NCSLC, which relies on there being a high enough percentage of altered DNA in the blood to be detected.[5] This test uses a methodology called droplet digital PCR (ddPCR) to analyze cell-free DNA and RNA to detect driver mutations in NSCLC for diagnosis or therapy monitoring. Both cell-free DNA testing and ddPCR methodology for detecting sequence variants are new molecular techniques that currently lack established analytical and clinical validity. Furthermore, high false negative rates being reported for circulating tumor DNA tests are of concern. In addition, although this test includes some genes with proven clinical utility for guiding targeted therapy for NSCLC (*EGFR*, *ALK*, *ROS1* and *BRAF*); it also includes genes which do not have proven clinical utility for directing treatment (*KRAS* and *RET*).
Guardant360 (Guardant Health)

The Guardant360 test is a circulating tumor cell assay that detects somatic point mutations in 73 genes identified across all solid tumor sites. This test also detects insertions and deletions in 23 genes, amplifications (CNVs) in 18 genes and fusions in six genes. This test is not specifically intended for NSCLC patients. This test uses ddPCR methodology. Both cell-free DNA testing and ddPCR methodology for detecting sequence variants are new molecular techniques that currently lack established analytical and clinical validity. Furthermore, high false negative rates being reported for circulating tumor DNA tests are of concern. In addition, although this test includes some genes with proven clinical utility for guiding

targeted therapy for NSCLC (*EGFR*, *ALK*, *ROS1* and *BRAF*); it also includes genes which do not have proven clinical utility for directing treatment for any indication, including NSCLC.

Proteomic Tests

A proteomic test is one that evaluates the expression of an individual's entire complement of proteins at any given time, using mass spectrometry or protein microarray methodologies. Proteomic testing has been proposed as a tool to predict response-to and selection-of targeted therapy for patients with survival outcomes NSCLC as well as predict survival outcomes. One example of a currently available proteomic test is described below.

VeriStrat® (Biodesix, Inc.)

The VeriStrat® test is a non-invasive blood-based test intended to provide predictive and prognostic proteomic information for patients with NSCLC who test negative for *EGFR* mutations or whose *EGFR* mutation status is unknown.[6] The test "measures a patient's response to a growing tumor and the chronic activation of complex proteomic pathways known to be associated with aggressive cancer" and classifies a patient's response as "good" or "poor". A VeriStrat "Poor" status is said to indicate more aggressive disease; while patients with a VeriStrat "Good" status are thought to have a more favorable prognosis. In addition, the test proposes to identify patients that may benefit from 1st-line platinum doublet therapy or *EGFR* TKI's.

Of note, Biodesix offers a test called Biodesix Lung Reflex® that combines both VeriStrat® and GeneStrat®. This would be considered a proteogenomic test, described below).

Proteogenomic Tests

Proteogenomic testing is a term describing a new type of molecular testing that simultaneously examines an individual's genome and proteome. These tests may use either tissue or blood samples and include analysis of DNA, the RNA and proteins. Currently this type of testing is primarily done in research settings. One example of a currently available proteogenomic test is described below.

GPS Cancer™ Test (NantHealth, Inc.)

GPS Cancer™ is a molecular test that integrates proteomics detected by mass spectrometry with whole genome (DNA) and whole transcriptome (RNA) sequencing, of both normal and cancer tissue.[7] This test is intended to inform personalized treatment strategies before treatment begins. The test assays protein biomarkers known to induce drug resistance or indicate drug sensitivity for chemotherapy, monoclonal antibody therapy, hormonal therapy, targeted therapy and immunotherapy. In addition, this test "includes whole genome sequencing of over 20,000 genes and 3 billion base pairs, and incorporates whole transcriptome sequencing of over 200,000 RNA transcripts".

REVIEW OF EVIDENCE

The evidence review below will focus on the clinical utility of molecular tests to determine whether testing improves treatment management or overall patient-relevant health outcomes.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of molecular testing to guide targeted therapy for metastatic stage IV NSCLC. Below is a summary of the available evidence identified through June 2021.

ALK Gene Testing

The clinical utility of testing for *ALK* gene rearrangements to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted in recent years on the use of genetic testing for *ALK* rearrangements to inform therapy with TKIs in patients with metastatic NSCLC.[6,8-14]

BRAF V600E Mutation Testing

The clinical utility of testing for mutations in the *BRAF* gene to guide *BRAF*-specific targeted therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted over the past five years on the use of genetic testing for *BRAF* V600E mutations to inform *BRAF*-specific targeted therapy in patients with metastatic NSCLC.[15-17]

Epidermal Growth Factor Receptor (*EGFR*) Gene Testing

The clinical utility of testing for small deletions in exon 19 and point mutations T790M and L858R in the *EGFR* gene to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous systematic reviews conducted over the past five years on the use of genetic testing of the *EGFR* gene to inform therapy with TKIs in patients with metastatic NSCLC.[18-28]

PD-L1 Protein Testing

The clinical utility of testing for PD-L1 protein expression to PD-1 pathway-specific immunotherapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted in recent years on the use of testing for PD-L1 protein expression PD-1 pathway-specific immunotherapy in patients with metastatic NSCLC.[29-35]

ROS1 Gene Testing

The clinical utility of testing for *ROS1* gene rearrangements to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted recent years on the use of genetic testing for *ROS1* rearrangements to inform therapy with TKIs in patients with metastatic NSCLC.[36-38]

Additional Actionable Genetic Targets for NSCLC

There is sufficient evidence of clinical utility for the following genetic alterations and their ability to guide targeted treatments for patients with metastatic NSCLC:

- *RET* gene rearrangements[39-42]
- MET gene amplifications and exon skipping point mutations (e.g. METex14)[43-49]
- *HER2* (also known as *ERBB2*) mutations[50-52]

This evidence has been published as clinical trials and nonrandomized studies conducted in recent years on NSCLC patients and are supported by strong NCCN recommendations despite not being FDA-approved for NSCLC at this time.

Other Genetic Alterations in NSCLC

The following tests or test components lack demonstrated clinical utility in patients with NSCLC:

- Uncommon alterations in *EGFR*, including insertions in exon 20 and point mutations: G719X, L861Q, and S768I [2,3,5,53-56]
- *KRAS* mutations[4,7,57-62]
- *PIK3CA* mutations[60]

Evidence regarding these molecular markers is limited by one or more of the following:

- Poor study design including:
    - small sample sizes of primary studies
    - heterogeneity in patient cohorts within and between studies, including heterogeneity in clinical variables including age, ethnicity, smoking status, staging, histological types
    - heterogeneity between trials in terms of treatment regimens administered based on molecular marker status
- Inconsistent or lack of association between positive marker status and prediction of drug efficacy, reported as disease control rate, progression free survival or overall survival.
- Inconsistent or lack of association between positive marker status and prognosis of survival, independent of therapy.

Therefore, the benefit of utilizing these molecular markers in patients with metastatic NSCLC remains unclear or unknown.

Expanded Genetic Tests

The evidence for clinical utility of expanded genetic panel tests performed on tumor tissue from NSCLC patients, including but not limited to the FoundationOne and FoundationOne CDx™ tests, Caris Molecular Intelligence (MI) Tumor Seek, and the Oncomine™ Dx Target test, are limited primarily to small prospective case series (n=3-25) and retrospective studies which used large expanded panels to identify molecular markers to guide targeted therapy.[39,42,63-65]

- Of note, one large retrospective review of genomic testing patterns in patients treated by 89 oncologists in two states within a three-year period reported on molecular profiling and subsequent impact on treatment for 814 patients with metastatic NSCLC.[66] The authors reported 59% of patients met current guideline recommendations for biomarker testing and 13% had insufficient tissue for genotyping. The authors concluded "genomic testing presents multiple logistical challenges for oncologists, including coordination of sample handling, long turnaround times, access to targeted therapies, insufficient tissue, and patient harm from the repeat biopsies necessary if the tissue sample is insufficient."

- In 2016 (archived 2018), Hayes published a review of the FoundationOne test and its ability to guide treatment decisions for patients with solid malignant cancers.[67] Regarding the tests' use in lung cancer, the review included one clinical utility study that included seven patients with NSCLC out of 103 patients evaluated.[68] Hayes deemed this study to be of poor quality and stated that the study provided limited evidence of the clinical impact of FoundationOne on decision-making. Although a majority of patients had a potentially actionable alteration, few received profile-guided treatment." Hayes rated the FoundationOne test as a "D2, insufficient evidence" for guiding treatment decisions for patients with solid malignant cancers, based on very low quality evidence of clinical validity and utility.

- In 2018 (updated 2020), Hayes published a molecular test assessment on FoundationOne CDx by Foundation Medicine Inc.[69] The assessment found no studies on the analytical validity, clinical validity, and clinical utility of the test. Hayes gave FoundationOne CDx a D2 rating for use as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies and to provide tumor mutation profiling or biomarkers with and without companion diagnostic claims to be used in patients with solid tumors.

- In 2017 (updated 2019), ECRIgene published a product brief on the FoundationOne CDx genomic profiling test for guiding targeted therapy for cancer, including 19 studies reporting clinical utility (8 retrospective and 10 prospective).[70] Although ECRI concluded that the "balance of evidence is somewhat favorable" for the use of the FoundationOne CDx test, only one of the clinical utility studies evaluated in the review included a small number of NSCLC patients.[64] In addition, ECRI stated that a "major limitation of the evidence base on FoundationOne was a paucity of studies directly comparing clinical outcomes of patients managed with and without FoundationOne test results."

  Overall, the evidence published on the use of expanded panel tests is limited by the following:

  - Lack of within-study comparator group (outcomes of patients managed with or without a particular test)
  - Lack of studies comparing outcomes between two different tests
  - Comparative studies with statistically significant differences in baseline clinical characteristics between groups

  Taken together, the benefit of utilizing expanded genetic panels to guide targeted therapy decisions in patients with metastatic NSCLC remains unclear.

Circulating Tumor DNA Tests

Due to uncertainties regarding the analytical and clinical validity of circulating tumor DNA tests for first-line targeted therapy guidance and to confirm targeted therapy resistance for patients with NSCLC, it is difficult to ascertain the clinical utility of circulating tumor DNA tests. Some tests (i.e. InVisionFirst-Lung®) are limited to studies assessing clinical and analytical validity.[71-75] The limited number of studies that have reported on measures of clinical utility for circulating tumor DNA tests performed on plasma samples from NSCLC patients, including but not limited to the GeneStrat®, Guardant360 and the Oncomine™ Lung cfDNA Assay tests are limited to small prospective case series (n=9-68).[66,76-80]

Evidence regarding the clinical utility of circulating tumor DNA testing is limited by one or more of the following:

- Body of evidence consists of case series and systematic reviews of these case series.
- Poor study design including:
  - The majority of primary studies are of small sample size (n=11-134)
  - Heterogeneous study populations in terms of clinical variables including age, ethnicity, smoking status, staging, histological types
- Larger case series were limited by multiple tissue DNA tests and circulating tumor DNA tests being performed on patients within each study cohort, making it difficult for studies to draw conclusions due to test heterogeneity.

- In 2016 (updated 2020), Hayes published a review of the Guardant360 test and its ability to identify actionable alterations across all solid tumor sites.[81] Actionable alterations were defined as "alterations, for which NCCN guidelines exist… which identifies FDA-approved treatments and clinical trials to help guide treatment decisions." In 3 studies evaluated, 8.9% to 28.4% of patients with NSCLC, breast cancer or diverse cancers received a matched targeted therapy based on variant(s) identified by Guardant360, with one retrospective data review study reporting that 26% of NSCLC patients had a change in targeted treatment after Guardant360 results. This study was also limited by its small sample size (n=116), lack of concordance comparison with tissue next generation sequencing, and investigators' financial conflicts of interest with Guardant Health. In 3 studies, the objective response rate ranged from 43% to 85.7% in patients with NSCLC or different solid tumors. One study reported a longer median progression-free survival in patients with NSCLC who received matched therapy based on Guardant360 results (14.7 months) compared with patients who never received matched therapy (7.8 months), although this difference was not statistically significant.

  Investigators concluded that, taken collectively, the 7 evaluated studies provided low-quality evidence in support of the clinical utility of the Guardant360 test, only 1 of which was a prospective study evaluating NSCLC. Hayes ultimately assigned Guardant360 a "C" rating ("potential but unproven benefit") as a tool to identify actionable alterations in solid tumors, based on very low quality evidence of clinical validity and utility.

- In 2017 (updated 2020), Hayes published a review of the GeneStrat test to detect driver variants for diagnosis, therapy selection, or therapy monitoring for patients with NSCLC.[82] The review identified one study that reported analytical and clinical validity, but did not identify any studies reporting on clinical utility. Therefore, Hayes rated the Genestrat test as a "D2, insufficient evidence" for all purposes including therapy selection and monitoring, based on very low quality evidence of clinical validity and a lack of studies on clinical utility.

While studies reporting clinical utility of molecular marker testing using circulating tumor DNA generally report patient specific health outcomes due to targeted therapy selection to be similar to that of markers found via tumor tissue tests, very few studies have reported on the concordance between these two methodologies to determine equivalent test performance. However, one large recent systematic review reported that sensitivity of circulating tumor DNA assays for NSCLC ranged from 56-65% and concordance with tissue testing was between 74-86%.[79] Therefore, the uncertainties concerning clinical validity and clinical utility preclude conclusions about whether molecular marker analysis from circulating tumor DNA can replace testing of tissue.

- In 2020, ECRI updated an evidence review evaluating the clinical validity and utility of Guardant360 in informing management of advanced solid tumor cancers.[83] Four studies on clinical validity and 10 studies on clinical utility were included in the review. Among the 4 clinical

validity studies, one cohort study reported on NSCLC, comparing Guardant360 with a tissue-sample, PCR-based test and found that Guardant360 had a sensitivity of 66% for identifying EDFR T790M mutations in patients with NSCLC compared to 51% for the cobas plasma test. One cohort study on clinical utility found that Guardant360 identified actionable genetic alterations in 48% of patients, and 0.6% received test-guided therapy. When comparing the group that received Guardant-guided therapy and a historical control group, no significant differences were found in objective response rate. Another observational study found that 13% of patients with AGAs received Guardant-guided therapy and overall survival was not statistically different when compared to nontargeted treatment.

Limitations included the lack of prospective study, lack of controls and surrogate outcomes. Investigators concluded that evidence supporting Guardant360's clinical utility was "somewhat favorable" but that additional controlled trials comparing outcomes after Guardant360 use to tissue NGS of NSCLC were needed. "Guardant360 identifies actionable genetic alterations (AGAs) in patients with non-small cell lung cancer (NSCLC) and other solid tumors and matches patients to targeted therapies that may improve outcomes. Available studies reported too few data to determine Guardant360-guided treatment's impact on overall survival (OS) or progression-free survival (PFS), but objective or partial responses occurred in some patients whose therapy was guided by test results."

- In 2019, Leighl and colleagues compared comprehensive cfDNA genotyping relative to physician discretion standard-of-care (SOC) tissue genotyping to identify guideline-recommended biomarkers in patients with metastatic non-small cell lung cancer (mNSCLC).[84] Prospectively enrolled patients with previously untreated mNSCLC undergoing physician discretion SOC tissue genotyping submitted a pretreatment blood sample for comprehensive cfDNA analysis (Guardant360.) Among 282 patients, clinically relevant NSCLC-associated biomarkers were detected at a similar rate as SOC testing, with the combination of tissue-based genotyping and cfDNA analysis resulting in a meaningfully higher frequency of identification of NSCLC driver mutations than either method alone. Tissue-based genotyping identified 67% (60/89) of the guideline-recommended biomarkers in first pass, with reflex cfDNA testing identifying the final 33%. In cases where cfDNA genotyping was utilized first, 87% (77/89) of the biomarkers were identified initially, with reflex tumor genotyping identifying the remaining 13%. The median TAT for cfDNA analysis was also significantly lower than that for SOC tumor genotyping (9 days vs. 15 days).

  Investigators concluded that cfDNA genotyping is a clinically viable alternative to obtaining guideline complete genotyping for first-line therapy selection in patients with advanced NSCLC. Limitations included heterogenous SOC tissue genomic assessments, author's financial conflicts of interest, and the inherent insensitivity of cfDNA sequencing among patients with lower metastatic burdens, due to the reduced shed of tumor DNA into the plasma.[85]

Proteomic Tests

Evidence regarding proteomic testing to guide treatment decisions and provide management-altering prognostic information for NSCLC has been focused primarily on the VeriStrat® assay. Studies reporting on the clinical utility of VeriStrat® are limited by one or more of the following:

- Body of evidence consists largely of retrospective analyses of clinical trials or physician treatment decisions.[86-88]
- Trials have been heterogeneous in terms of:
    - Evaluating the test for first-line, second-line or third line therapy guidance
    - Treatment regimens used
    - Patient population characteristics
- Trials have reported inconsistent associations of VeriStrat® status with survival outcomes.[51,89,90]

In 2020, Hayes published a review of the VeriStrat® test for prognostic use in patients with advanced NSCLC.[82] The review included 2 studies that assessed analytical validity, 6 studies that assesses clinical validity, and 2 studies that assessed clinical utility. No studies reported on the current commercially available Veristrat test's analytical validity, but the 2 included studies reported on aspects of the test, showing the test to be reproducible. Among the 6 studies assessing clinical validity, some evidence has shown that the Veristat test has prognostic and predictive value. Patients with a VS Good test results had significantly improved progression-free and overall survival compared to patients with a VS Poor test result, irrespective of administered treatment. Evidence also suggests that patients with VS Good test results had better survival outcomes when treated with EDGR TKI therapy rather than placebo or chemotherapy, while there was no difference in outcomes among patient with VS Poor test results. Hayes notes that these clinical validity studies had a number of limitations, including retrospective study design in 5 of 6 studies, lack of placebo control, not powered for the analyses conducted, and unrepresentative patient selections. The 2 studies evaluated for clinical utility through the test's impact on physician treatment recommendations. Both studies showed that test results influenced physician decisions, yet they did not directly evaluate patient health outcomes and studies were industry funded, offering very-low-quality evidence for the clinical utility of the test.

Hayes rated VeriStrat® test as a "C" for use of the VeriStrat test, stating, "Although there is some published evidence regarding the analytical validity of the test and clinical validity of the test's classifications to be associated with patients' overall survival and progression-free survival, the impact on health outcomes has not been demonstrated."[82]

Therefore, the benefit of utilizing proteomic tests in patients with metastatic NSCLC remains unclear.

Proteogenomic Tests

Evidence regarding proteogenomic testing to guide treatment decisions and provide management-altering prognostic information for oncologic indications has been focused primarily on the GPS Cancer™ test. Very few studies have reported on the use of proteogenomic tests for diagnosis or prognosis. Studies are needed to standardize and validate proteogenomic testing methods, and once this has been established, the clinical validity and utility of proteogenomic testing can be adequately evaluated. To date, there are no studies reporting on the clinical validity or clinical utility of the GPS Cancer™ test for NSCLC or any other indication. Therefore, the benefit of utilizing proteogenomic tests in patients with metastatic NSCLC is unknown.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The NCCN non-small cell lung cancer (NSCLC) clinical practice guidelines (v3.2022) recommend the following for evaluation of metastatic NSCLC:[1]

- "…(T)he following biomarkers should be tested including *EGFR* mutations, *BRAF* mutations, *ALK* fusions, *ROS1* fusions, *METex14* skipping mutations, *RET* rearrangements, and PD-L1 expression levels."
- To minimize wasting of tissue, NCCN recommends broad molecular profiling be done as part of biomarker testing using validated panel tests, which assess a minimum of the following potential genetic variants: *EGFR* mutations, *BRAF* mutations, *ALK* fusions and *ROS1* fusions simultaneously, be performed.
- Patients may have rare driver mutations such as *HER2* (*ERBB2*) mutations, *RET* gene rearrangements, MET gene amplifications, or MET mutations; for which these are targeted that are NOT FDA-approved for NSCLC.
    - NCCN recommends these tests to guide targeted therapy in these situations, indicating that there is sufficient evidence that these therapies are effective for patients with metastatic NSCLC.
    - Although NCCN considered these tests to guide "emerging" therapies, they provided a category 2A recommendation for these genetic alterations and specific therapies.
- NCCN acknowledges that in many patients only small biopsy samples may be acquired (typically using minimally invasive methods), and therefore judicious use of tests such as immunohistochemistry for protein analysis and/or diagnosis is recommended in order to conserve tissue for molecular studies.
    - Based on limited tissue samples, NCCN indicates the use of broader molecular profiling tests using a number of appropriate methods (next generation sequencing, multiplex mutation screening, and fluorescent in situ hybridization [FISH]) for markers that have FDA-approved therapies.

  - NCCN recommends broader molecular profiling of genes other than *EGFR*, *BRAF*, *ALK* and *ROS1* may be performed for use in context of clinical trials, but does not address any specific tests by name.

- NCCN states that testing for the *EGFR* mutation in patients who have progressed on first line therapies may be done using a plasma biopsy (also known as cell-free DNA testing or liquid biopsy) if there is insufficient tumor sample left for testing. However, if the plasma biopsy is negative then re-biopsying tumor tissue is recommended if feasible. This statement was based on two small trials (n=58 and 60) which used plasma samples to detect *EGFR* mutations, and one plasma genotyping validation study (n=180 patients). Although the positive predictive value was 79% (one study) and the sensitivity of plasma assays for the T790M mutation ranged from 70-77% (two studies), the test was also reported to have a 30% false negative rate, indicating that tumor biopsy tissue is needed for T790M genotyping.
- NCCN states that circulating tumor DNA (from blood, also known as liquid biopsy or cell-free DNA) can be considered in specific clinical circumstances, most notably:
  - If a patient is medically unfit for invasive tissue sampling; **or**
  - In the initial diagnostic setting, following pathologic confirmation of a NSCLC diagnosis, there is insufficient material for molecular analysis and follow-up tissue-based analysis is planned for patient in which an oncogenic driver is not identified; **or**
  - In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available.

<u>American Society of Clinical Oncology (ASCO)</u>

In 2018, ASCO endorsed recommendations published by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) regarding molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors.[91] After making a few small modifications to the 2018 CAP/IASLS/AMP guidelines, ASCO recommended the following:[92]

- The following testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics:

  - *EGFR* mutation testing (neither IHC for expression nor fluorescent or chemiluminescent in situ hybridization for copy number should be used)
  - *ROS1* rearrangement testing (IHC may be used, but a positive IHC result must be confirmed by a molecular or cytogenetic method)
  - *BRAF* mutation testing
  - *ALK* rearrangement testing (IHC or FISH may be used)

- The following tests are not recommended as routine stand-alone assays outside of the context of a clinical trial: *RET*, *HER2* (*ERBB2*), and MET testing.

- There is insufficient evidence to support the use of circulating tumor cell molecular analysis (also known as cell-free [CF] DNA, plasma genotyping or liquid biopsy) to identify *EGFR* mutations for targeted therapy use.

POLICY SUMMARY

There is sufficient evidence that genetic testing of certain genetic alterations in the ALK, *EGFR, BRAF, ROS1, RET, MET and/or HER2* genes and/or testing for PD-L1 protein expression provides guidance for targeted therapies for metastatic non-small cell lung cancer (NSCLC) that lead to improvements in progression free and overall survival. In addition, current U.S-based clinical guidelines recommend the testing of these molecular targets in this patient population. However, there is insufficient evidence of clinical utility and a lack of support by clinical practice guidelines for the testing of additional mutations in the genes noted above, for other genes including *KRAS* or *PIK3CA*, and more comprehensive molecular testing, including expanded gene panels, circulating tumor DNA tests, and proteomic and proteogenomic tests.

Low-quality but consistent evidence supports the use of circulating-free tumor DNA (also known as cell-free [CF] DNA, plasma genotyping or liquid biopsy) to identify mutations in patients who meet specific criteria.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.
The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

U.S. Food & Drug Administration (FDA)

According to the FDA, "a companion diagnostic device can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product."[6]
Of note, companion diagnostic tests are approved by the FDA based on sufficient clinical validity, as reported as adequate test performance measures like sensitivity, specificity, positive predictive values and/or negative predictive values. FDA-approval does not require evidence of clinical utility.

List of U.S. FDA Cleared or Approved Companion Diagnostic Tests

Device (Test) Trade Name	Device Manufacturer	Drug Trade Name (Generic Name)	Intended Use (IU) / Indications for Use (IFU)
cobas® *EGFR* Mutation Test	Roche Molecular Systems, Inc	TARCEVA® (erlotinib)	Markers: *EGFR* L858R mutation and Exon 19 deletions Test specimens: DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.
cobas® *EGFR* Mutation Test v2	Roche Molecular Systems, Inc	TARCEVA® (erlotinib)	Markers: *EGFR* L858R mutation and Exon 19 deletions Test specimens: DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood. Note: Safety and efficacy of TARCEVA® (erlotinib) has not been established for the following EGFR mutations also detected by the cobas® EGFR Mutation Test v2: G719X, Exon 20 insertions, T790M, S768I and L861Q.
cobas® *EGFR* Mutation Test v2	Roche Molecular Systems, Inc	IRESSA® (gefitinib)	Markers: *EGFR* L858R mutation and Exon 19 deletions Test specimens: DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.

Device (Test) Trade Name	Device Manufacturer	Drug Trade Name (Generic Name)	Intended Use (IU) / Indications for Use (IFU)
			Note: Safety and efficacy of IRESSA® (gefitinib) has not been established for the following EGFR mutations also detected by the cobas® EGFR Mutation Test v2: G719X, Exon 20 insertions, T790M, S768I and L861Q.
cobas® *EGFR* Mutation Test v2	Roche Molecular Systems, Inc	TAGRISSO™ (osimertinib)	Marker: *EGFR* T790M and L858R mutations and Exon 19 deletions. Test specimens: Formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood. Notes: • The efficacy of TAGRISSO® (osimertinib) has not been established in the EGFR T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained. • Note: Safety and efficacy of TAGRISSO™ (osimertinib) has not been established for the following EGFR mutations also detected by the cobas® EGFR Mutation Test v2: G719X, Exon 20 insertions, S768I and L861Q.
FoundationOne CDx™ (F1CDx)	Foundation Medicine, Inc.	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)	*Markers: EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations Test specimens: DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue
FoundationOne CDx™ (F1CDx)	Foundation Medicine, Inc.	Tagrisso® (osimertinib)	*Marker: EGFR* exon 20 T790M alterations Test specimens: DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue
FoundationOne CDx™ (F1CDx)	Foundation Medicine, Inc.	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)	*Marker: ALK* gene rearrangements Test specimen: DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue

Device (Test) Trade Name	Device Manufacturer	Drug Trade Name (Generic Name)	Intended Use (IU) / Indications for Use (IFU)
FoundationOne CDx™ (F1CDx)	Foundation Medicine, Inc.	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)	*Marker: BRAF* V600E Test specimen: DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue
Oncomine™ Dx Target	Life Technologies Corporation	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)	Marker: *BRAF* V600E Test specimen: DNA from formalin- fixed, paraffin-embedded (FFPE) tumor tissue samples
Oncomine™ Dx Target	Life Technologies Corporation	XALKORI® (crizotinib)	Marker: *ROS1* fusions Test specimen: RNA isolated from formalin- fixed, paraffin-embedded (FFPE) tumor tissue samples
Oncomine™ Dx Target	Life Technologies Corporation	IRESSA® (gefitinib)	Marker: *EGFR* L858R mutation and Exon 19 deletions Test specimen: DNA isolated from formalin- fixed, paraffin-embedded (FFPE) tumor tissue samples
PD-L1 IHC 22C3 pharmDx	Dako North America, Inc.	KEYTRUDA® (pembrolizumab)	Marker: PD-L1 protein Test specimen: formalin-fixed, paraffin-embedded (FFPE) tissue Note: The specimen should be considered to have PD-L1 expression if TPS ≥1% and high PD-L1 expression if TPS ≥50%.
PD-L1 (SP142)	Ventana Medical Systems, Inc.	Tecentriq (atezolizumab)	Marker: PD-L1 protein Test specimen: formalin-fixed, paraffin-embedded (FFPE) tissue Note: PD-L1 expression in >= 50% tumor cells or >= 10% tumor-infiltrating immune cells determined by VENTANA PD-L1 (SP142) Assay in NSCLC tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab). See the TECENTRIQ® product label for PD-L1 expression cutoff values guiding therapy in specific clinical circumstances.
therascreen *EGFR* RGQ PCR Kit	Qiagen Manchester, Ltd.	Iressa (gefitinib)	Markers: *EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations

Device (Test) Trade Name	Device Manufacturer	Drug Trade Name (Generic Name)	Intended Use (IU) / Indications for Use (IFU)
			Test Specimen: DNA derived from formalin-fixed paraffin-embedded (FFPE) NSCLC tumor tissue. Note: Safety and efficacy of Iressa (gefitinib) have not been established in patients whose tumors have L861Q, G719X, S768I, and exon 20 insertions, and T790M mutations, which are also detected by the therascreen *EGFR* RGQ PCR Kit.
therascreen *EGFR* RGQ PCR Kit	Qiagen Manchester, Ltd.	Gilotrif® (afatinib)	Markers*: EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations Test Specimen: DNA derived from formalin-fixed paraffin-embedded (FFPE) NSCLC tumor tissue. Note: Safety and efficacy of GILOTRIF (afatinib) have not been established in patients whose tumors have L861Q, G719X, S768I, and exon 20 insertions, and T790M mutations, which are also detected by the therascreen *EGFR* RGQ PCR Kit.
therascreen *EGFR* RGQ PCR Kit	Qiagen Manchester, Ltd.	Vizimpro (dacomitinib)	Markers*: EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations Test Specimen: DNA derived from formalin-fixed paraffin-embedded (FFPE) NSCLC tumor tissue. Note: Safety and efficacy of Vizimpro (dacomitinib) have not been established in patients whose tumors have L861Q, G719X, S768I, and exon 20 insertions, and T790M mutations, which are also detected by the therascreen *EGFR* RGQ PCR Kit.
VENTANA ALK (D5F3) CDx Assay	Ventana Medical Systems, Inc.	XALKORI® (crizotinib) or ZYKADIA® (ceritinib)	Marker: Anaplastic lymphoma kinase (ALK) protein Test Specimen: Formalin-fixed, paraffin-embedded (FFPE) tissue
VYSIS ALK Break Apart FISH Probe Kit	Abbott Molecular Inc.	Xalkori® (crizotinib)	*Marker: ALK* gene rearrangements Test specimen: DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue

Notes:

- FDA approval of a companion diagnostic test does not guarantee coverage per this medical policy. All molecular tests addressed in this policy, whether FDA- and/or Clinical Laboratory Improvement Amendments (CLIA)-approved, must have demonstrated clinical utility for all components of the test. See Policy Guidelines above for the definition of clinical utility.
    - For example, there may be one or more FDA-approved companion diagnostic tests that allow for testing of circulating-free tumor DNA (cfDNA) from plasma for somatic indications. However, there is insufficient evidence, at this time, that testing for somatic mutations from plasma is an effective method of testing compared to testing of tumor tissue.
- This list is current as of 6/30/2021.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

POLICY CROSS REFERENCES

Health Plans Medical Policies

- Circulating Tumor Cell and DNA Assays For Cancer Management
- Genetic Counseling
- Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business Except Medicare)

Health Plans Pharmacy Policies

- Injectable ANTI-Cancer Medications. Antineoplastics, ORPTCONC102
- Oral ANTI-Cancer Medications. Antineoplastics, ORPTCONC103

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