MEDICAL POLICY	**Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (Medicare Only)**
Effective Date: 4/01/2022  4/01/2022 Medical Officer Date	Medical Policy Number: 193 Medical Policy Committee Approved Date: 5/18; 3/19; 3/2020; 6/2020; 07/2020; 12/2020; 3/2021; 7/2021; 10/2021; 11/2021; 3/2022

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:

Medicare only

MEDICARE POLICY CRITERIA

The following Centers for Medicare & Medicaid Service (CMS) guidelines should be utilized for medical necessity coverage determinations. Click the link provided in the table below to access applicable medical necessity criteria. All listed guidelines apply.

Service	Medicare Guidelines
Next generation sequencing tests *(FDA approved or cleared CDx tests)*	National Coverage Determination (NCD) for Next Generation Sequencing (NGS) (90.2) ***Note:** This NCD is limited to NGS *DNA* sequencing tests which are FDA-approved or cleared as a companion diagnostic (CDx) test **and** only when used for cancer-related purposes. These include the following: • FoundationOne CDx™ (F1CDx) (0037U or 81479 [CPT 81455 used for claims between 3/16/18 and 3/31/18]) (Foundation Medicine, Inc.) • FoundationOne®Liquid CDx (0239U or 81479, the latter code used for claims prior to 7/1/2020) (Foundation Medicine) • Guardant360® CDx (0242U) (Guardant Health, Redwood City, CA)

	• Oncomine™ Dx Target Test (0022U) (Thermo Fisher Scientific) *(See also the LCA for Billing and Coding: MolDX: ThermoFisher Oncomine Dx Target Test for Non-Small Cell Lung Cancer [A55888] for this test)* For all other tests, including tests which are **not** FDA-approved or cleared as a CDx test, tests which have a specific LCD or LCA available, NGS *RNA* sequencing tests, or for tests related to *non*-cancer indications, see separate Medicare references below or separate Medicare policies.
***Next generation sequencing tests** (**non**-plasma based testing, for tests (not otherwise specified in this policy)* *(**Non**-FDA approved or cleared CDx tests)*	***See "Policy Guidelines" for specific panel test information.*** • Testing performed in OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY: LCD for MolDX: Next-Generation Sequencing for Solid Tumors (L38121) • Testing performed in CA or NV: LCD for MolDX: Next-Generation Sequencing for Solid Tumors (L38119) • Testing performed in NC, SC, AL, GA, VA, WV: LCD for MolDX: Next-Generation Sequencing for Solid Tumors (L38045) All of the above LCDs require successful completion of a technical assessment (TA) by the MolDX Program contractor. See "Policy Guidelines" for specific panel test information. If a test is not listed in this policy, further research may be required.
Plasma based genomic profiling panel tests for solid tumors** (not otherwise specified in this policy**) *(**Non**-FDA approved or cleared CDx tests)*	Testing performed in NC, SC, AL, GA, VA, KY, OH, WV, AK, ID, OR, WA, UT, AZ, MT, ND, SD, WY, CA and NV: LCD for MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043) *(Since several Medicare contractors use MolDX guidance policies, the LCD L38043 will be used until a corresponding LCD for each service area is effective and final. Once each service area's LCD is final, it will replace L38043 for the respective service area.)* While Guardant360® is one such test named specifically, according to the LCD, "Other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®." Tests must be listed on the DEX™ Change Healthcare Registry website as a potentially covered test by MolDX for Medicare. If a test is not listed in this policy, further research may be required.
EGFR Testing	Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, WY: Local Coverage Article: Billing and Coding: MolDX: FDA-Approved EGFR Tests (A54424)
Guardant360® (Guardant Health, Inc.; Redwood City, CA)	Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, WY: Local Coverage Article: Billing and Coding: Guardant360® (A58192)

InVisionFirst®-Lung (Inivata; Research Triangle Park, NC)	Local Coverage Determination (LCD): MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer (L37899)
PGDx elio™ tissue complete (0250U) (Personal Genome Diagnostics, Inc.; Maryland) *VeriStrat® (CPT 81538)*	Novitas Local Coverage Determination (LCD): Biomarkers for Oncology (L35396) *For the GDx elio™ tissue complete test: According to this LCD, "Peer-reviewed full manuscript evidence is required to support combination panels for multiple biomarkers, particularly regarding their alleged composite clinical validity/utility. For example; such potential billing for multiple, diverse biomarkers (e.g., diagnostic/monitoring/prognostic/predictive) can only achieve medical necessity when it is clearly evident how each requested biomarker can be individually contributory." Therefore, each biomarker must have documentation supporting use for the individual patient. If documentation does not support how each biomarker will directly contribute to the member's care, the test is considered not medically reasonable or necessary.* *For the VeriStrat® test: Search the LCD for the test by name.*
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets™ (MSK-IMPACT™) (0048U) (Memorial Sloan Kettering; New York)	LCD: Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (L37810)
DetermaRX™ (Oncocyte Corp.) (0288U; California)	For testing performed in services areas which have adopted MolDX guidelines, the MolDX Program requires laboratories to submit a technology assessment (TA) to establish analytical and clinical validity (AV/CV), and clinical utility (CU). *(Noridian LCA A54552)* The outcome of MolDX TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog. If a test does **not** have a coverage determination, clinical validity or utility has not been established via the TA review process and the test **not considered medically reasonable and necessary** under *SSA §1862(a)(1)(A)* until a MolDX review is complete and coverage is indicated by MolDX or Noridian. The DetermaRX™ is a test which has not yet undergone the required TA review to establish clinical utility.

POLICY GUIDELINES

Companion Diagnostic Devices (In Vitro and Imaging Tools)

Please see the FDA website "List of Cleared or Approved Companion Diagnostic Devices" for the most current information on these tests and new tests as they are approved.

PLEASE READ: The MolDX Program requires laboratories to submit a technology assessment (TA) to establish analytical and clinical validity (AV/CV), and clinical utility (CU). *(Noridian LCAs A54554 and A54552)* reimbursement is only allowed for "approved tests… for dates of service consistent with the effective date of the coverage determination" after MolDX review. *(Noridian LCDs L36256 and L35160)*

The outcome of MolDX TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog. Genetic tests noted as "covered" within this registry may potentially be medically reasonable and necessary when all other Medicare coverage requirements are met, including criteria found in LCDs or LCAs.

In contrast, if a test does **not** have a coverage determination, clinical validity or utility has not been established via the TA review process and the test **not considered medically reasonable and necessary** under *SSA §1862(a)(1)(A)* until a MolDX review is complete and coverage is indicated by MolDX or Noridian.

Related panel tests include:

Note: This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MolDX Program contractor.

Proprietary Test Name	Laboratory	MolDX TA Review Outcome (as found in the DEX™ Diagnostics Exchange registry catalog)
Oncotype MAP Pan-Cancer Tissue test (0244U)	Paradigm Diagnostics (Arizona) (Test may be billed by Genomic Health)	Covered
The Resolution ctDx Lung™ (0179U)	Resolution Bioscience (Washington)	Covered
Oncomine™ Lung cfDNA Assay	Thermo Fisher Scientific	Not covered
DetermaRX™ (0288U)	Oncocyte Corp. (California)	Not covered

BILLING GUIDELINES

For additional coding and billing guidance, see related local coverage articles (LCAs):

- Local Coverage Article: Billing and Coding: MoIDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer (A57665)

Next Generation Sequencing Tests and NCD 90.2

Based on Transmittal #10832 (Change Request 12124), included in NCD 90.2, the following CPT codes are considered appropriate for billing for the FDA-approved companion diagnostic tests for NSCLC.[1]

NGS Test	Code
FoundationOne CDx (F1CDx)	81455 (3/16/18 - 3/31/18) 0037U (4/1/18 to present)
FoundationOne®Liquid CDx	81479 (8/26/20 to 12/31/20) 0239U (1/1/21 to present)
Oncomine Dx Target Test	0022U
Guardant360® CDx	81479 (8/7/20-3/31/21) 0242U (4/1/21 to present)

CPT CODES

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

Medicare Only	
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
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
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)
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
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue
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
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
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
No Prior Authorization Required The following codes do not require routine review for medical necessity, but they may be subject to audit.	
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)
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
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

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

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.

MEDICAL POLICY CROSS REFERENCES

Providence Health Plans Medical Policies

- Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (All Lines of Business Except Medicare)
- Circulating Tumor Cell and DNA Assays For Cancer Management
- Genetic and Molecular Testing (Medicare Only)

Providence Health Plans Pharmacy Policies

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

REFERENCES

1. CMS Manual System Department of Health & Human Services (DHHS), Pub 100-20 One-Time Notification Centers for Medicare & Medicaid Services (CMS) Transmittal 10832 Change Request 12124; Date: June 2, 2021; Link: https://www.cms.gov/files/document/r10832OTN.pdf