Medicare Medical Policy

Circulating Tumor Cell and DNA Assays for Cancer Management

MEDICARE MEDICAL POLICY NUMBER: 306

Effective Date: 4/1/2023

Last Review Date: 3/2023

Next Annual Review: 6/2023

INSTRUCTIONS FOR USE: Company Medicare Medical Policies serve as guidance for the administration of plan benefits and do not constitute medical advice nor a guarantee of coverage. Company Medicare Medical Policies are reviewed annually to guide the coverage or non-coverage decision-making process for services or procedures in accordance with member benefit contracts (otherwise known as Evidence of Coverage or EOCs) and Centers of Medicare and Medicaid Services (CMS) policies, manuals, and other CMS rules and regulations. In the absence of a CMS coverage determination or specific regulation for a requested service, item or procedure, Company policy criteria or applicable utilization management vendor criteria may be applied. These are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. 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.

The Company reserves the right to determine the application of Medicare Medical Policies and make revisions to these policies at any time. Any conflict or variance between the EOC and Company Medical Policy will be resolved in favor of the EOC.

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”).

PRODUCT AND BENEFIT APPLICATION

☒ Medicare Only

MEDICARE COVERAGE CRITERIA

IMPORTANT NOTE: More than one Centers for Medicare and Medicaid Services (CMS) reference may apply to the same health care service, such as when more than one coverage policy is available (e.g., both an NCD and LCD exist). All references listed should be considered for coverage decision-making. The Company uses the most current version of a Medicare reference available at the time of publication; however, these websites are not maintained by the Company, so Medicare references and their corresponding hyperlinks may change at any time. If there is a conflict between the Company Medicare Medical Policy and CMS guidance, the CMS guidance will govern.

NOTE: This policy does not address cell-free DNA tests (also known as circulating tumor DNA tests or liquid biopsies) for targeted therapies for **non-small cell lung cancer**. (See Cross References section below)

Service	Medicare Guidelines
Circulating tumor cell (CTC) testing	• **Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY:** Local Coverage Determination (LCD) for MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells (L38645) • **Testing performed in CA and NV:** LCD for MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells (L38643) *If a test is not specifically included in a policy, additional research may be required to ensure all elements of the LCD are met for coverage.*
Next Generation Sequencing Tests – Plasma-Based Tests Subject to NCD 90.2	National Coverage Determination (NCD) for Next Generation Sequencing (NGS) (90.2) **NOTE:** Relevant tests subject to this NCD include the following: • 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) *(See additional rows below as well as "Policy Guidelines" for notes regarding other Guardant360 test options.)*

	See "Policy Guidelines" below for important information regarding the NCD 90.2
All Other Plasma Based (liquid biopsy) Testing	For the Guardant360 LDT® (0326U): • Local Coverage Article (LCA): Billing and Coding: Guardant360® (A58192) *(See separate row for the FDA approved CDx test)* For all other plasma-based (liquid biopsy) tests: • **Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY:** LCD: MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L39232) • **Testing performed in CA and NV:** LCD: MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L39230) • **Testing performed in NC, SC, AL, GA, VA, and WV:** LCD: MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043)* **NOTES:** According to the above LCDs, "Other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®." Therefore, liquid biopsy tests **other than** Guardant360® may also be medically necessary; however, if a test is not specifically called out in a policy, additional research is required to confirm Medicare coverage as not all liquid biopsy tests will meet LCD requirements.
	This list of tests are considered **not medically necessary**, based on Medicare guidelines (see *"Policy Guidelines"* below) and the above LCD(s). • LungLB® (LungLife AI®) (Code 0317U; California) • HelioLiver™ Test (California) (Code 0333U; Fulgent Genetics, LLC and Helio Health Inc.) • RadTox™ cfDNA test (DiaCarta Clinical Lab) (Code 0285U; California) • ColoScape™ Colorectal Cancer Detection cfDNA test (DiaCarta Clinical Lab) (Code 0368U; California) *If a test is not specifically included in a policy, additional research may be required.*
PIK3CA Gene Tests	**Testing performed in NC, SC, AL, GA, VA, WV, AK, ID, OR, WA, UT, AZ, MT, ND, SD, WY, CA and NV:** LCA: Billing and Coding: MolDX: PIK3CA Gene Tests (A55200)

Colvera (Code 0229U)	LCA for Billing and Coding: Biomarkers for Oncology (A52986)
Tests Not Otherwise Addressed *Examples:* • *CELLSEARCH® Circulating Multiple Myeloma Cell (CMMC) Test (Menarini Silicon Biosystems, Inc.) (Code 0337U)* • *CELLSEARCH® HER2 Circulating Tumor Cell (CTC-HER2) Test (Menarini Silicon Biosystems, Inc.) (Code 0338U)* • *IMMray® PanCan-d (Immunovia, Inc.) (Code 0342U)* • *NavDx® (Naveris, Inc.; Massachusetts) (Code 0356U)*	Company medical policy for Circulating Tumor Cell and DNA Assays for Cancer Management I. These services are considered **not medically necessary** for Medicare based on the Company medical policy. *See Policy Guidelines below.*

IMPORTANT NOTICE: While some services or items may appear medically indicated for an individual, they may also be a direct exclusion of Medicare or the member's benefit plan. Such excluded services or items by Medicare and member EOCs include, but are not limited to, services or procedures considered to be cosmetic, not medical in nature, or those considered not medically reasonable or necessary under *Title XVIII of the Social Security Act, §1862(a)(1)(A).* If there is uncertainty regarding coverage of a service or item, please review the member EOC or submit a pre-service organization determination request. Note that the Medicare Advance Beneficiary Notice of Noncoverage (ABN) form **cannot** be used for Medicare Advantage members. *(Medicare Advance Written Notices of Non-coverage. MLN006266 May 2021)*

POLICY CROSS REFERENCES

MEDICAL POLICIES

- Genetic and Molecular Testing, MP317

PHARMACY POLICIES

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

The full Company portfolio of Medicare Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to review for medical necessity under *Social Security Act, §1862(a)(1)(A),* the following documentation **must** be provided. If any of these items are not submitted, the review may be delayed, and the decision outcome could be affected:

- Laboratory name and location.
- Test name (if appropriate, the proprietary test name, especially for panel tests) and relevant CPT code(s)
    - Non-specific (e.g., 81401, 81402, etc.) or unlisted (e.g., 81479) CPT codes are not sufficient to satisfy this requirement alone. Test/gene description or name is required.
- Documented diagnosis of a recurrent, relapsed, refractory, metastatic, or advanced solid tumor.
- Documentation of any prior genetic or molecular testing performed for the individual.
- Documentation of cancer treatments being considered for the individual, meeting both of the following:
    - The patient must be a candidate for further treatment; and
    - The drug must be:
        - FDA-approved for that patient's cancer ***OR*** have a National Comprehensive Cancer Network (NCCN) 1 or NCCN 2A recommendation for that patient's cancer, and
        - The FDA-approved indication or NCCN recommendation must be based on information about the presence or absence of a genetic biomarker tested for in the test (i.e., the medication being considered must be indicated for tumors that rely on relevant gene mutation or variant test results. Medications or cancer treatment that are not dependent on genetic test results would not require the use of genetic testing to proceed with such treatment decisions, thus resulting in genetic testing not being medically necessary to proceed with such treatments).
- Documentation of either no prior cancer treatments for the cancer being tested ***OR*** documentation of prior cancer treatments that have been used with the noted response to those treatments.
- Tissue based testing:
    - Documentation must support tissue-based, comprehensive genomic profiling (CGP) is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated); or
    - For NSLC, documentation that tissue-based CGP did not show actionable mutations.

GUARDANT360® TESTS

Guardant offers multiple "Guardant360®" test options. Only the Guardant360® CDx test has been FDA approved (as of August 2020). All other Guardant tests are lab-developed tests without FDA approval. In addition, the Guardant360 TissueNext™ test is **not** a liquid biopsy, and therefore, this medical policy would **not** apply to this test.

IMPORTANT INFORMATION REGARDING NEXT GENERATION SEQUENCING (NGS) TESTS AND NCD 90.2

The Medicare national coverage determination (NCD) 90.2 does **not** apply to all NGS tests. The scope of this NCD is limited to next generation sequencing tests, NGS *DNA* sequencing tests that are used for cancer-related purposes and only tests which have received FDA-approval or clearance as a companion diagnostic (CDx) test (see Criteria 1b and 2b of the NCD). The FDA website "List of Cleared or Approved Companion Diagnostic Devices" provides the most current listing of FDA-approved or cleared tests.

Other NGS tests are **not** subject to this NCD. This includes:

- Tests which are not next generation sequencing tests;
- Tests which do not have FDA-approval or clearance as CDx tests;
- NGS *RNA* sequencing tests; and
- Tests related to *non*-cancer indications.

Coverage of tests which are not subject to the NCD is left to local Medicare Contractor (MAC) discretion. Some tests may or may not have a specific LCD or LCA available, while others are subject to more generalized requirements. See Medicare references in the "Criteria" table above or separate Medicare policies. If a test is not specifically included in a policy, additional research may be required to confirm coverage under Medicare.

MEDICARE AND MEDICAL NECESSITY FOR DIAGNOSTIC LABORATORY SERVICES

Laboratories performing tests in service areas which have adopted guidelines or coverage determinations made by the Medicare Molecular Diagnostics (MolDX) Program contractor are required to submit a technology assessment (TA) to establish analytical and clinical validity (AV/CV) and clinical utility (CU). Supporting LCDs regarding TA reviews include, but are not limited to, the following:

- Laboratories in CA & NV: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35160)
- Laboratories in NC, SC, GA, TN, AL, VA, & WV: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L35025)
- Laboratories in AK, ID, OR, WA, UT, AZ, MT, ND, SD, & WY: LCD for MolDX: Molecular Diagnostic Tests (MDT) (L36256)

Coverage or non-coverage determinations made by MolDX are maintained in the DEX™ Diagnostics Exchange registry catalog and are available for public viewing. If a test does not have a coverage determination by the MolDX Program, then AV/CV and CU have **not** been established and the test is considered not medically reasonable and necessary under *SSA §1862(a)(1)(A)* until a MolDX review is complete and coverage is indicated by MolDX or Noridian. Therefore, tests identified in this policy as not meeting this requirement are not medically reasonable or necessary for Medicare under *SSA §1862(a)(1)(A).* This includes both the RadTox™ cfDNA test and the ColoScape™ Colorectal Cancer Detection cfDNA test, both by DiaCarta Clinical Lab in California. These tests are listed in the DEX Registry as "Not covered" for Medicare which means these tests have had their clinical utility and analytical validity (CU/AV) assessed and were determined to be not medically reasonable or necessary for Medicare under *Social Security Act, §1862(a)(1)(A).*

MEDICARE AND GENERAL MEDICAL NECESSITY

The Company policy for *PHA Medicare Medical Policy Development and Application* (MP50) provides details regarding Medicare's definition of medical necessity and the hierarchy of Medicare references and resources during the development of medical policies, as well as the Plan's use of evidence-based processes for policy development. In the absence of Medicare coverage policies (e.g., manual, national coverage determination [NCD], local coverage determination [LCD], article [LCA], etc.), Medicare regulatory guidelines do allow Medicare Advantage Organizations (MAOs) to make their own coverage

determinations, as long as the MAO applies an objective, evidence-based process, based on authoritative evidence. *(Medicare Managed Care Manual, Ch. 4, §90.5)*
Following an evidence-based assessment of current peer-reviewed medical literature, the Company may consider certain medical services or technologies to be "investigational." The term "investigational" is not limited to devices or technologies which have not received the appropriate governmental regulatory approval (e.g., U.S. Food and Drug Administration [FDA]), but rather may also mean the procedure, device, or technology does not meet all of the Company's technology assessment criteria, as detailed within the Company policy for *Definition: Experimental/Investigational* (MP5).

Only medically reasonable and necessary services or items which treat illness or injury are eligible for Medicare coverage, as outlined in *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. Thus, services which lack scientific evidence regarding safety and efficacy because they are investigational are "not medically reasonable or necessary" for Medicare Plan members. *(Medicare Claims Processing Manual, Ch. 23, §30 A)*

REGULATORY STATUS

U.S. FOOD & DRUG ADMINISTRATION (FDA)

While clearance by the Food and Drug Administration (FDA) is a prerequisite for Medicare coverage, the 510(k) premarket clearance process does not in itself establish medical necessity. Medicare payment policy is determined by the interaction of numerous requirements, including but not limited to, the availability of a Medicare benefit category and other statutory requirements, coding and pricing guidelines, as well as national and local coverage determinations and clinical evidence.

BILLING GUIDELINES AND CODING

GENERAL

See associated local coverage articles (LCAs) for additional coding and billing guidance.

- LCA: Billing and Coding: MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells (A58185)
- LCA: Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Tumors (A58975)
- LCA: Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Tumors (A58973)

CODES*		
CPT	0155U	PIK3CA (phosphatidylinositol-hyphen4,5-hyphenbisphosphate 3-hyphenkinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y)
	0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-hyphen4,5-hyphenbisphosphate 3-hyphenkinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis *(Used for the Colvera® test, by Clinical Genomics Pathology, Inc.)*

	0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
	0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer
	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
	0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
	0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood
	0342U	Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline
	0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
	0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer *(Used to report the ColoScape™ Colorectal Cancer Detection test by DiaCarta Clinical Lab)*
	81309	PIK3CA (phosphatidylinositol-hyphen4, 5-hyphenbiphosphate 3-hyphenkinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
	81479	Unlisted Molecular Pathology
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood)
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required
HCPCS	None	

***Coding Notes:**

- The code list above is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit. According to Medicare, "presence of a payment amount in the MPFS and the Medicare physician fee schedule database (MPFSDB) does not imply that CMS has determined that the service may be covered by Medicare." The issuance of a CPT

or HCPCS code or the provision of a payment or fee amount by Medicare does **not** make a procedure medically reasonable or necessary or a covered benefit by Medicare. *(Medicare Claims Processing Manual, Chapter 23 - Fee Schedule Administration and Coding Requirements, §30 - Services Paid Under the Medicare Physician's Fee Schedule, A. Physician's Services)*

- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

None

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
1/2023	Q1 2023 code updates (converted to new format 2/2023)
4/2023	Q2 2023 code update (added code 0368U); corrected criteria applied to RadTox™ cfDNA