

Liquid Biopsy



INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Disclaimer

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Related Medicare Advantage Medical/Pharmacy Coverage Policies

Comprehensive Genomic Profiling for Hematologic Malignancies

Comprehensive Genomic Profiling for Solid Tumors

Genetic Testing for Diagnosis and Monitoring of Cancer

Measurable (Minimal) Residual Disease Testing

Related Documents

Please refer to [CMS website](#) for the most current applicable National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Type	Title	ID Number	Jurisdiction Medicare	Applicable States/Territories
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			Administrative Contractors (MACs)	
NCD	Generation Sequencing (NGS)	90.2		
LCD	MolDX: Inivata™, InvisionFirst®, Liquid Biopsy for Patients with Lung Cancer	L37903		
LCD	MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells	L38584	J15 - CGS Administrators, LLC	KY, OH
LCD	MolDX: Plasma-Based Genomic Profiling in Solid Tumors	L38065		
LCD	MolDX: Inivata™, InvisionFirst®, Liquid Biopsy for Patients with Lung Cancer	L37921		
LCD	MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells	L38678	J5, J8 - Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
LCD	MolDX: Plasma-Based Genomic Profiling in Solid Tumors	L38168		
LCD	MolDX: Inivata™, InvisionFirst®, Liquid Biopsy for Patients with Lung Cancer	L37987		
LCD	MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells	L38643	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
LCD	MolDX: Plasma-Based Genomic Profiling in Solid Tumors	L39230		
LCD	MolDX: Inivata™, InvisionFirst®, Liquid Biopsy for Patients with Lung Cancer	L37899		
LCD	MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells	L38645	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
LCD	MolDX: Plasma-Based Genomic Profiling in Solid Tumors	L39232		

LCD	MolDX: Inivata™, InvisionFirst®, Liquid Biopsy for Patients with Lung Cancer	L37870		
LCD	MolDX: Plasma-Based Genomic Profiling in Solid Tumors	L38043	JJ, JM - Palmetto GBA	AL, GA, NC, SC, TN, VA, WV
LCD	Biomarkers for Oncology	L35396	JH – Novitas Solutions, Inc.	AK, LA, CO, DE, D.C., MD, MS, NJ, NM, OK, PA, TX
LCD	Molecular Pathology Procedures	L35000	J6 - National Government Services, Inc.	IL, MN, WI

Description

Liquid biopsy is a test usually performed on blood samples but may be performed on other body fluid samples. It purportedly analyzes the presence of cancer cells released from a tumor that are circulating or fragments of deoxyribonucleic acid (DNA) from tumor cells in the fluid. It may be used to manage treatment, assist in drug selection, determine prognosis as well as therapy response and be used as a minimally invasive alternative to tumor biopsy. The test may have the potential to detect cancer at an early stage. Liquid biopsy may identify 2 main biomarkers in an individual with cancer:

- Circulating cell-free DNA (cfDNA), also known as circulating tumor DNA (ctDNA) are DNA fragments from a tumor that circulate in the blood or body fluid of an individual who has cancer. Examples of ctDNA tests include, but may not be limited to, FoundationOne Liquid, Guardant360, Tempus xF; **OR**
- Circulating tumor cells (CTCs) are cancer cells that detach from the primary tumor and travel through the bloodstream or lymphatic system to other parts of the body. Examples of CTC tests include, but may not be limited to, CellSearch

Liquid biopsy test may also analyze additional biomarkers such as autoantibodies, cell free ribonucleic acid (RNA) and tumor antigens. These are purported to have the potential to stratify cancer risk or diagnose cancer at an early stage.

Coverage Determination

iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test

identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary's specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the [MolDX program](#) and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare's reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

Guardant360 Testing

Guardant360 (0326U) will be considered medically reasonable and necessary when all the following requirements are met:

- Individual has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system. Individuals who would meet all of the indications on the Food & Drug Administration (FDA) label for larotrectinib if they are found to have a neurotrophic receptor tyrosine kinase (NTRK) mutation may be considered to have advanced cancer; **AND**
- Tissue-based, comprehensive genomic profiling (CGP) is infeasible (quantity not sufficient for tissue based CGP or invasive biopsy is medically contraindicated) **or** specifically in non-small cell lung cancer (NSCLC) Tissue-based CGP has shown no actionable mutations; **AND**
- Individual has not previously been tested with the Guardant360 test for the same genetic content. For an individual who has been tested previously using Guardant360 for cancer, that individual may not be tested again unless there is clinical evidence that the cancer has evolved wherein testing would be performed for different genetic content. Specifically, in an individual with previously tested cancer, who have evidence of new malignant growth despite response to a prior targeted therapy, that growth may be considered sufficiently genetically different to require additional genetic testing; **AND**
- Individual is untreated for the cancer being tested, or the individual is not responding to treatment (eg, progression or new lesions on treatment); **AND**
- The individual has decided to seek further cancer treatment with the following conditions:
 - Individual is a candidate for further treatment with a drug that is either FDA approved for the individual's cancer, or has a National Comprehensive Cancer Network (NCCN) 1 or NCCN 2A recommendation for that individual's cancer; **AND**
 - The FDA approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360 assay

Circulating Tumor Cells Testing

Circulating tumor cells (CTCs) testing including, but not limited to, **CellSearch (86152, 86153)** will be considered medically reasonable and necessary when all the following requirements are met:

- Individual has been diagnosed with cancer; **AND**
- The specific cancer type has an associated biomarker that can be tested using CTCs; **AND**
- Tissue based testing for the specific biomarker is infeasible (quantity not sufficient or invasive biopsy is medically contraindicated) **OR** will not provide sufficient information for subsequent medical management (eg, in cases where human epidermal growth factor receptor 2 (HER2) overexpression is negative in a tissue biopsy but may be positive in the CTCs, due to tumor heterogeneity). There is clear documentation of at least 1 of these reasons for testing in the medical record; **AND**
- At least 1 of the following criteria are met **AND** there is clear documentation of at least 1 of these in the medical record:
 - Individual's cancer has not previously been tested for the specific biomarker; **OR**
 - Individual has newly metastatic cancer, and a metastatic lesion has not been tested for the specific biomarker; **OR**
 - Individual demonstrates signs of clinical, radiological or pathologic disease progression; **OR**
 - There is concern for resistance to treatment based on specific and well-established clinical indications; **AND**
- The CTC-based biomarker test meets the following criteria to establish the test as reasonable and necessary:
 - The clinical validation has demonstrated performance that is equivalent or superior to tissue-based testing or another already accepted test for the same biomarker for the same intended use; **AND**
 - Clinical validity (for new analytes) must be established through studies published in the peer-reviewed literature for the intended use of the test in the intended population; **AND**
- For a given encounter, only 1 test for assessing the biomarker may be performed **UNLESS** a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test

InVisionFirst Testing

InVisionFirst (0388U) will be considered medically reasonable and necessary when the following requirements are met:

- Diagnosed with advanced (Stage IIIB/IV) NSCLC; **AND either of the following:**

At diagnosis:

- When results for EGFR single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and SNVs for BRAF are not available; **AND**
- Tissue-based CGP is infeasible (quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated)

OR

At progression:

- For an individual progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR SNVs and indels; rearrangements in ALK and ROS1; and SNVs for BRAFs, **AND**
 - Tissue-based CGP is infeasible; **OR**
 - Progression on EGFR tyrosine kinase inhibitors (TKIs)

General Liquid Biopsy Testing Criteria

Liquid biopsy (eg, cfDNA, ctDNA) including, but not limited to, **FoundationOne Liquid CDx (0239U)**, **Guardant360 CDx (0242U)** will be considered medically reasonable and necessary when all the following requirements are met:

- Individual diagnosed with either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; **AND**
- Tissue based, CGP is infeasible (quantity not sufficient for tissue based CGP or invasive biopsy is medically contraindicated); **AND**
- Individual has not been previously tested with the same test using next generation sequencing (NGS) for the same cancer genetic content; **AND**
- Decided to seek further cancer treatment (eg, therapeutic chemotherapy); **AND**
- The diagnostic laboratory test using NGS must have:
 - FDA approval or clearance as a companion in vitro diagnostic; **AND**
 - FDA approved or cleared indication for use in that individual's cancer; **AND**

- Results provided to the treating physician for management of the individual using a report template to specify treatment options

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

[US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage](#)

The following tests may not be considered a benefit (statutory exclusion)⁷³:

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**
- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following **services/items** will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the [MoIDX Program](#)
- Liquid and solid tumor tissue testing for the same diagnosis and same genetic content
- Duplicate testing of the same biomarker (from the same sample type and for the same clinical indication)

using different methodologies is not covered

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Screening services such as presymptomatic genetic tests and services used to detect and undiagnosed diseased or disease predisposition are not a Medicare benefit and are not covered.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis	
81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements	
81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability	
81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	
81479	Unlisted molecular pathology procedure	
81599	Unlisted multianalyte assay with algorithmic analysis	
82378	Carcinoembryonic antigen (CEA)	
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	
86304	Immunoassay for tumor antigen, quantitative; CA 125	
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk	
0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result	
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)	
0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis	
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	
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	
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	
0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer	
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	
0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection	
0395U	Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease	
0397U	Oncology (non-small cell lung cancer), cell-free DNA from plasma, targeted sequence analysis of at least 109 genes, including sequence variants, substitutions, insertions, deletions, select rearrangements, and copy number variations	
0405U	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected	

0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability	
0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected	
0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer	
CPT® Category III Code(s)	Description	Comments
No code(s) identified		
HCPCS Code(s)	Description	Comments
No code(s) identified		

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Change Summary

- 01/01/2024 New Policy.