ONCOLOGY: CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS (LIQUID BIOPSY)

OVERVIEW

Cell-free circulating tumor DNA (ctDNA) originates directly from the tumor tissue (primary or metastasis); as tumor cells die the contents are released into the bloodstream. Genetic tests performed on cell-free circulating tumor DNA (ctDNA), also referred to as a liquid biopsy, potentially offer a noninvasive alternative to tissue biopsy for detection of “driver mutations”, or acquired genetic mutations that may guide targeted therapy, and may also be used to track progression of disease.

Circulating tumor cells (CTCs) are intact tumor cells that are shed from tumor cells into the bloodstream or lymphatic system. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic rather than for guiding therapeutic choices, through quantification of circulating levels.

POLICY REFERENCE TABLE

Coverage Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)				
Comprehensive Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)	FoundationOne® Liquid CDx (Foundation Medicine)	0239U	C15, C16, C25, C34	1, 2, 6, 7, 8, 10, 14
	Guardant360® CDx (Guardant Health)	0242U		
	Guardant360® LDT (Guardant Health)	81455		
	NeoLAB® Solid Tumor Liquid Biopsy (NeoGenomics Laboratories)			
	Tempus xF: Liquid Biopsy Panel of 105			

	Genes (Tempus)			
	PlasmaSELECT 64 (Personal Genome Diagnostics)			
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung™ (Resolution Biosciences, LabCorp, Integrated Oncology)	0179U	C34	1, 10, 14
	OncoBEAM™ Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc)	81210, 81235, 81275, 81276		
	Non-Small Cell Lung Cancer Expanded Profile (Biocept)	81445		
	InVisionFirst®-Lung Liquid Biopsy (inivata)			
Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ CRC1: KRAS, NRAS, BRAF, HRAS (Sysmex Inostics, Inc)	81210, 81275, 81276, 81311	C18-C20	3, 10
	Colorectal Cancer Profile (Biocept)	81210, 81275, 81276		
Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ Melanoma1: BRAF, NRAS (Sysmex Inostics, Inc)	81210, 81311	D03, D43	4, 10
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)				
EGFR Variant Analysis via ctDNA	cobas® EGFR Mutation Test v2	81235	C34	1, 10, 14, 15, 16
	OncoBEAM™ Lung1: EGFR (Sysmex Inostics, Inc)			
	EGFR Exon 18, 19, 20, 21, Mutation Analysis Blood and Cell-Free DNA (Mayo Medical Laboratories)			
	Cell-Free DNA EGFR T790M Mutation Analysis Blood (Mayo Medical Laboratories)			
	EGFR T790M Mutation Detection in ctDNA (ARUP Laboratories)			
	EGFR T790M Mutation Detection Blood (University of Washington Medical Center)			
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600 Test (Mayo Medical Laboratories)	81210	C18-C20, C24, C43,	3, 4, 10

	OncoBEAM™ Melanoma2: BRAF (Sysmex Inostics, Inc)		C71, C73, C91.4	
	Melanoma Cancer Profile (Biocept)			
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81275, 81276	C18-C20	3, 10
NRAS Variant Analysis via ctDNA	NeoLAB® NRAS Mutation Analysis - Liquid Biopsy (NeoGenomics Laboratories)	81311	C18-C20	3, 10
PIK3CA Variant Analysis via ctDNA	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	0177U	C50	5, 10
	PIK3CA Mutation CDx (NeoGenomics Laboratories)	81309		
Circulating Tumor Cell (CTC) Tests				
AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)	AR-V7 Prostate Cancer (Johns Hopkins Medical Institutions - Pathology Laboratory)	81479	C61, Z19.2	2, 11, 12, 13
	OncotypeDx AR-V7 Nucleus Detect (Genomic Health Inc.)			
Circulating Tumor Cell (CTC) Enumeration Analysis	Circulating Tumor Cells (CTC) for Colorectal Cancer by CellSearch (Mayo Medical Laboratories)	86152, 86153, S3711	C00.0-C96.9	5, 9
	Circulating Tumor Cells for Prostate Cancer by CellSearch (Mayo Medical Laboratories)			
	Circulating Tumor Cells (CTC) Count (Biocept)			

OTHER RELATED POLICIES

This policy document provides coverage criteria for circulating tumor DNA (ctDNA) and circulating tumor cells testing (liquid biopsy). For other oncology-related testing, please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.

- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.
- ***Oncology: Algorithmic Testing*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to circulating tumor DNA or circulating tumor cell testing that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

MOLECULAR PROFILING PANEL TESTS VIA CIRCULATING TUMOR DNA (ctDNA)

Comprehensive Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)

I. Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 81455) are considered **medically necessary** when:

A. The member has a diagnosis of one of the following:

1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**
2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**
3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**
4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

5. Locally advanced / metastatic pancreatic adenocarcinoma, **OR**
6. Gastric cancer, **OR**
7. Esophageal or Esophagogastric Junction cancer, **OR**
8. Metastatic prostate cancer, **OR**
9. Metastatic colorectal cancer, **AND**

B. The member is a candidate for an anti-cancer therapy, **AND**

C. At least one of the following:

1. The member is medically unfit for invasive tissue sampling (biopsy), **OR**
2. The member does not have a biopsy-amenable lesion.

II. Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 81455) are considered **investigational** for all other indications.

III. Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 81455) performed simultaneously with, or subsequent to, solid tumor tissue testing is considered **investigational**.

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Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)

I. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81276, 81445) are considered **medically necessary** when:

A. The member has a diagnosis of any of the following:

1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**
2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**

3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**

4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**

B. The member is a candidate for an anti-cancer therapy, **AND**

C. At least one of the following:

1. The member is medically unfit for invasive tissue sampling (biopsy), **OR**

2. The member does not have a biopsy-amenable lesion.

II. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81276, 81445) are considered **investigational** for all other indications.

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Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)

I. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81276, 81311) are considered **medically necessary** when:
   A. Member has metastatic colorectal cancer, **AND**
   B. Panel includes *KRAS, NRAS and BRAF* analysis.

II. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81276, 81311) for all other indications are considered **investigational**.

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Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)

I. Melanoma focused panel tests via circulating tumor DNA (ctDNA) (81210, 81311) are considered **investigational**.

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SINGLE GENE MOLECULAR PROFILING PANEL TESTS VIA CIRCULATING TUMOR DNA (ctDNA)

EGFR Variant Analysis via ctDNA

I. *EGFR* variant analysis (81235) via cell-free circulating tumor DNA (ctDNA) is considered **medically necessary** when:

   A. The member has a diagnosis of any of the following:

      1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**

      2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**

      3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**

      4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**

   B. The testing is being done at time of diagnosis or at the time of progression, **AND**

   C. Treatment with an *EGFR* tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) is being considered, **AND**

   D. At least one of the following:

      1. The member is medically unfit for invasive tissue sampling (biopsy), **OR**

      2. The member does not have a biopsy-amenable lesion.

II. *EGFR* variant analysis (81235) via cell-free circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational** for all other indications.

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BRAF Variant Analysis via ctDNA

I. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational**.

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KRAS Variant Analysis via ctDNA

I. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational**.

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NRAS Variant Analysis via ctDNA

I. *NRAS* variant analysis (81311) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational**.

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PIK3CA Variant Analysis via ctDNA

I. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA) is considered **medically necessary** when:

   A. The member has recurrent or stage IV hormone receptor-positive/ HER2-negative breast cancer.

II. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational** for all other indications.

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CIRCULATING TUMOR CELL TESTS

AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)

I. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **medically necessary** when:

   A. The member has metastatic castration-resistant prostate cancer (M1 CRPC), **AND**

   B. The member has had a progression after first-line treatment with enzalutamide (Xtandi®) or abiraterone (Zytiga®).

II. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **investigational** for all other indications.

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Circulating Tumor Cell (CTC) Enumeration

I. Circulating tumor cell (CTC) enumeration (86152, 86153, S3711) is considered **investigational**.

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NOTES AND DEFINITIONS

Cell-free circulating tumor DNA (ctDNA) is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

Circulating Tumor Cells (CTCs) are intact cells that have shed into the bloodstream or lymphatic system from a primary tumor or a metastasis site, and are carried around the body by blood circulation.

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CLINICAL CONSIDERATIONS

Cell-free circulating tumor DNA analysis should not be used in lieu of a histologic tissue diagnosis, however there are specific clinical considerations, outlined above, where the use of ctDNA may be considered.

Cell-free circulating tumor DNA analysis should not be performed simultaneously with tissue testing of a solid tumor.

If cell-free circulating tumor DNA analysis is negative, follow-up with tissue-based analysis is recommended.

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BACKGROUND AND RATIONALE

Practice Guidelines and Committee Statements

National Comprehensive Cancer Network (NCCN):

Non-Small Cell Lung Cancer

NCCN guidelines (v.4.2021) support the use of cell-free circulating tumor DNA (ctDNA) testing if a patient is either not medically fit for invasive tissue sampling, or if there is insufficient tissue for molecular analysis. If ctDNA testing is negative, there should be follow-up with tissue-based analysis. NCCN recognizes that studies have shown generally high sensitivity, but a significantly compromised sensitivity with up to 30% false-negative rate and does not support the use of ctDNA testing in lieu of a histologic tissue diagnosis, if it is possible and feasible.

Prostate Cancer

NCCN guidelines (v.1.2022) suggest the consideration of AR-V7 tests to help guide selection of therapy for patients with disease progression in the post-abiraterone/enzalutamide metastatic castration resistant prostate cancer setting.

NCCN guidelines (v.1.2022) strongly advocates evaluating tumor for alterations in homologous recombination DNA repair genes in individuals with metastatic prostate

cancer and states that ctDNA assay is an option when biopsy for histologic and molecular evaluation is not possible.

Colorectal Cancer

NCCN guidelines (V1.2022) state that RAS, BRAF, and HER2 amplification can be tested by individual genes or as part of a next generation sequencing panel, and either by tissue or blood-based assay

Melanoma

NCCN guidelines (v.2.2021) do not currently have a recommendation for the use of circulating tumor DNA (ctDNA) for patients with melanoma.

Breast Cancer

NCCN guidelines (v.2.2021) states that PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy) and if liquid biopsy is negative, tumor tissue testing is recommended.

NCCN guidelines (v.2.2021) recognize that patients with metastatic breast cancer and persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS; however, while CTC count has prognostic ability, it has failed to show a predictive value at this time.

Gastric Cancer

NCCN guidelines (v.2.2021) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management, and that the DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clone with altered treatment response profiles. NCCN also cautions the interpretation of negative results, as it does not exclude the presence of tumor mutation or amplifications that are clinically relevant.

Pancreatic Cancer

NCCN guidelines (v.2.2021) state that while testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible.

Esophageal or Esophagogastric Junction Cancer

NCCN guidelines (v.2.2021) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management,

and that the DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clone with altered treatment response profiles. NCCN also cautions the interpretation of negative results, as it does not exclude the presence of tumor mutation or amplifications that are clinically relevant.

American Society of Clinical Oncology and College of American Pathologists

The American Society of Clinical Oncology and College of American Pathologists (2018) published a joint review on the use of circulating tumor DNA analysis in patients with cancer, concluding the following:

> "The evidence indicates that testing for ctDNA is optimally performed on plasma collected in cell stabilization or EDTA tubes, with EDTA tubes processed within 6 hours of collection. Some ctDNA assays have demonstrated clinical validity and utility with certain types of advanced cancer; however, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer. Evidence shows discordance between the results of ctDNA assays and genotyping tumor specimens and supports tumor tissue genotyping to confirm undetected results from ctDNA tests. There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial. Given the rapid pace of research, re-evaluation of the literature will shortly be required, along with the development of tools and guidance for clinical practice."

The ASCO (2016) made the following guideline in regard to the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer:

> "The clinician should not use circulating tumor cells to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: strong."

College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (2018) published a guideline on molecular testing for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors and noted the following recommendations regarding liquid

biopsy for activating EGFR mutations and a consensus opinion regarding liquid biopsy for the T790M resistance mutation:

- Recommendation: "In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify [activating] EGFR mutations."
- Expert Consensus Opinion: "Physicians may use plasma cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative."
- No recommendation: "There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of EGFR T790M mutations at the time of EGFR TKI resistance."

U.S. Food and Drug Administration (FDA)

Cobas EGFR Mutation Test v2:

“On June 1, 2016, the U. S. Food and Drug Administration approved cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.) using plasma specimens as a companion diagnostic test for the detection of exon 19 deletions or exon 21 (L858R) substitution mutations in the epidermal growth factor receptor (EGFR) gene to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with Tarceva® (erlotinib). The cobas EGFR Mutation Test v2 is already approved for this indication using formalin-fixed paraffin-embedded (FFPE) tissue specimens. The new use is for detection of these specific mutations in circulating-free tumor DNA (cfDNA) isolated from plasma specimens, also called liquid biopsy specimens, to aid physicians in identifying patients who may be treated first with TARCEVA (erlotinib). This is the first “liquid biopsy test” approved for use by FDA. This new test may benefit patients who may be too ill or are otherwise unable to provide a tumor specimen for EGFR testing. Patients positive by cobas EGFR Mutation Test v2 using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are candidates for treatment with Tarceva (erlotinib). Patients who are negative by this test should undergo routine biopsy and testing for EGFR mutations with the FFPE tissue sample type.”

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