

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, 9
	Guardant360® CDx (Guardant Health)	0242U		
	Guardant360® 83+ genes (Guardant Health)	0326U		
	Guardant360® LDT (Guardant Health)	81455		
	NeoLAB® Solid Tumor Liquid Biopsy			

	(NeoGenomics Laboratories)			
	Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus)			
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung™ (Resolution Biosciences, LabCorp, Integrated Oncology)	0179U	C34	1
	OncoBEAM™ Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc)	81210, 81235, 81275, 81479		
	Non-Small Cell Lung Cancer Expanded Profile (Biocept)			
	InVisionFirst®-Lung Liquid Biopsy (inivata)	81479		
Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ CRC1: KRAS, NRAS, BRAF, HRAS (Sysmex Inostics, Inc)	81210, 81275, 81311, 81403, 81479	C18-C21	3
	Colorectal Cancer Profile (Biocept)	81405, 81406		
Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ Melanoma1: BRAF, NRAS (Sysmex Inostics, Inc)	81210, 81311, 81479	D03	4
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)				
EGFR Variant Analysis via ctDNA	OncoBEAM™ Lung1: EGFR (Sysmex Inostics, Inc)	81235, 81479	C34	10, 11
	EGFR T790M Mutation Detection in ctDNA (ARUP Laboratories)	81235		
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600 Test (Mayo Medical Laboratories)	81210	C18-C21, C43,	3, 4, 9
	OncoBEAM™ Melanoma2: BRAF (Sysmex Inostics, Inc)			
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81275, 81276	C18-C20	3, 9
PIK3CA Variant Analysis via ctDNA	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	0177U	C50	5
	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
	OncotypeDx AR-V7 Nucleus Detect (Exact Sciences Laboratories)			
Circulating Tumor Cell (CTC) Enumeration Analysis	Circulating Tumor Cells for Prostate Cancer by CellSearch (Univ of Michigan-Michigan Medical Genetics Laboratories)	86152, 86153	C00.0-C96.9	5
	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.

[back to top](#)

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, 0326U, 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, 0326U, 81455) are considered **investigational** for all other indications.
- III. Comprehensive molecular profiling panel tests via [circulating tumor DNA](#) (liquid biopsy) (0239U, 0242U, 0326U, 81455) performed simultaneously with, or subsequent to, solid tumor tissue testing is considered **investigational**.

[back to top](#)

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, 81479) 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. Biopsy was performed but material was insufficient for molecular analysis, **OR**
 3. Biopsy was performed but molecular analysis was not able to be completely assessed on tissue due to availability of testing methodologies
- II. Lung cancer focused panel tests via [circulating tumor DNA](#) (ctDNA) (0179U, 81210, 81235, 81276, 81479) are considered **investigational** for all other indications.

[back to top](#)

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

- I. Colorectal cancer focused panel tests via [circulating tumor DNA](#) (ctDNA) (81210, 81275, 81311, 81403, 81405, 81406, 81479) 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, 81311, 81403, 81405, 81406, 81479) for all other indications are considered **investigational**.

[back to top](#)

Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)

- I. Melanoma focused panel tests via [circulating tumor DNA](#) (ctDNA) (81210, 81311, 81479) are considered **investigational**.

[back to top](#)

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

EGFR Variant Analysis via ctDNA

- I. *EGFR* variant analysis (81235, 81479) 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 (examples: 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. Biopsy was performed but material was insufficient for molecular analysis, **OR**
 3. Biopsy was performed but molecular analysis was not able to be completely assessed on tissue due to availability of testing methodologies

- II. *EGFR* variant analysis (81235, 81479) via [cell-free circulating tumor DNA](#) (ctDNA), as a stand alone test, is considered **investigational** for all other indications.

[back to top](#)

***BRAF* Variant Analysis via ctDNA**

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

[back to top](#)

***KRAS* Variant Analysis via ctDNA**

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

[back to top](#)

***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.

[back to top](#)

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.

[back to top](#)

Circulating Tumor Cell (CTC) Enumeration

- I. [Circulating tumor cell \(CTC\)](#) enumeration (86152, 86153) is considered **investigational**.

[back to top](#)

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.

[back to top](#)

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.

[back to top](#)

BACKGROUND AND RATIONALE

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

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer guidelines (4.2022) 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 (p. MS-6).

NCCN Gastric Cancer guidelines (2.2022) 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 (p. GAST-B 5 of 6)

NCCN Pancreatic Adenocarcinoma guidelines (1.2022) state that while testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. PANC-1A).

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2022) 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 (p. ESOPH-B 5 of 6).

NCCN Colon Cancer guidelines (1.2022) 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 (p. COL-4)

NCCN Non-Small Cell Lung Cancer guidelines (4.2022) 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 (p. NSCL-H 7 of 7).

American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP)

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

“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.”

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

National Comprehensive Cancer Network (NCCN)

NCCN Non-Small Cell Lung Cancer guidelines (4.2022) 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 (p. NSCL-H 7 of 7).

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

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (1.2022) 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 (p. COL-4)

Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

NCCN Cutaneous Melanoma guidelines (3.2022) state that molecular testing on biopsied tissue is preferred, but can be performed on peripheral blood if tumor issue is unavailable (p. MEC-3 of 8).

EGFR Variant Analysis via ctDNA

College of American Pathologists, International Association for the Study of Lung Cancer, and 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."

US Food and Drug Administration (FDA)

"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."

PIK3CA Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (4.2022) 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 (p. BINV-R 1 of 3)

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

NCCN Prostate Cancer guidelines (4.2022) 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 (p. PROS-15A).

Circulating Tumor Cells (CTC) Enumeration Analysis

NCCN Breast Cancer guidelines (4.2022) 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 (p. MS-75).

[back to top](#)

REFERENCES

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[back to top](#)