Medica Central Coverage Policy

Policy Name:	**Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) MP9609**
Effective Date:	**January 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

Cell-free circulating tumor DNA (ctDNA or cfDNA) originates directly from the tumor tissue (primary or metastasis). As tumor cells die the contents are released into the bloodstream. Genetic tests performed on 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.
Cell-free circulating tumor DNA analysis should not be used in lieu of a histologic tissue diagnosis, however there are specific clinical considerations, outlined below, 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, with the exception of lung cancer.
If cell-free circulating tumor DNA analysis is negative, follow-up with tissue-based analysis is recommended.

POLICY REFERENCE TABLE

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)				
Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)	FoundationOne Liquid CDx (Foundation Medicine)	0239U	C15, C16, C18, C25, C34, C61	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16
	Guardant360 CDx (Guardant Health)	0242U		
	Guardant360 83+ genes (Guardant Health)	0326U		
	NeoLAB Solid Tumor Liquid Biopsy (NeoGenomics Laboratories)	81445, 81455, 81462, 81463, 81464		
	Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus)			
		0409U		
	LiquidHALLMARK (Lucence Health)			
	Caris Assure (Caris Life Sciences)	0485U		
	Northstar Select (BillionToOne)	0487U		
	OptiSeq Dual Cancer Panel Kit (DiaCarta, Inc)	0499U		
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung (Labcorp)	0179U	C34	1
	OncoBEAM Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc.)	81210, 81235, 81275, 81479		
	InVisionFirst-Lung Liquid Biopsy (NeoGenomics)	0388U		
	GeneStrat NGS (Biodesix)	81462		
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)				
EGFR Variant	EGFR T790M Mutation Detection,	81235	C34	1, 9

Coverage Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Analysis via ctDNA	Blood (University of Washington Medical Center - Laboratory Medicine-Genetics Laboratory)			
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600, Blood (Mayo Medical Laboratories)	81210	C18-C21, C43	3, 4, 8
	BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR (ARUP Laboratories)			
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81275, 81276	C18-C20	3, 8
PIK3CA Variant Analysis via ctDNA	therascreen PIK3CA RGQ PCR Kit (QIAGEN)	0177U	C50	5
	Cell-Free DNA PIK3CA Test, Blood (Mayo Medical Laboratories)	81309		
Circulating Tumor Cell (CTC) Tests				
AR-V7 Circulating Tumor Cells (CTC) Analysis	AR-V7 (Epic Sciences)	81479	C61	17
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH Circulating Tumor Cell (CTC) Test (CELLSEARCH)	86152	C00.0-C96.9	5,17
	CELLSEARCH Circulating Melanoma Cell (CMC) Test (Menarini Silicon)	0490U		
	CELLSEARCH ER Circulating Tumor Cell (CTC-ER) Test (Menarini Silicon)	0491U		
	CELLSEARCH PD-L1 Circulating Tumor Cell (CTC-PDL1) Test (Menarini Silicon)	0492U		

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 and Molecular 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)

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

I. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 0409U, 81445, 81455, 81462, 81463, 81464) are considered **medically necessary** when:

A. The member has a diagnosis, progression, or recurrence of one of the following:

1. Stage IV or metastatic lung adenocarcinoma, **OR**
2. Stage IV or metastatic large cell lung carcinoma, **OR**
3. Stage IV or metastatic squamous cell lung carcinoma, **OR**
4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Locally advanced/metastatic pancreatic adenocarcinoma, **OR**
6. Metastatic or advanced gastric cancer, **OR**
7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**
8. Metastatic prostate cancer, **OR**
9. Stage III or higher cutaneous melanoma**, OR**
10. Metastatic colorectal cancer, **OR**
11. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
12. Persistent or recurrent cervical cancer**, OR**
13. Unresectable or metastatic biliary tract cancer**, OR**
14. Suspected or confirmed histiocytic neoplasm, **OR**
15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR**
16. Locoregional unresectable or metastatic large or small cell carcinoma, **OR**

17. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm**, OR**

18. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**

19. Recurrent ovarian, fallopian tube or primary peritoneal cancer**, OR**

20. Recurrent or stage IV breast cancer, **AND**

B. If a broad molecular profiling panel test via circulating tumor DNA is being performed simultaneously with solid tumor tissue testing, the member must have one of the following diagnoses:

1. Lung adenocarcinoma, **OR**

2. Large cell lung carcinoma, **OR**

3. Squamous cell lung carcinoma, **OR**

4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

II. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455, 81462, 81463, 81464) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.

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, 0388U, 81210, 81235, 81275, 81462, 81479) are considered **medically necessary** when:

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

1. Advanced or metastatic lung adenocarcinoma, **OR**

2. Advanced or metastatic large cell lung carcinoma, **OR**

3. Advanced or metastatic squamous cell lung carcinoma, **OR**

4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

II. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 0388U, 81210, 81235, 81275, 81462, 81479) are considered **investigational** for all other indications.

back to top

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

***EGFR* Variant Analysis via ctDNA**

I. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA) is considered **medically**

necessary when:

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

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

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

II. *EGFR* variant analysis (81235) via 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) is considered **medically necessary** when**:**

A. The member meets one of the following:

1. The member has metastatic colorectal cancer, **AND**
   a) Testing for *NRAS* and *KRAS* is also being performed, either as separate tests or as part of a panel, **OR**
2. The member has stage III or higher cutaneous melanoma, **AND**
   a) Is being considered for adjuvant or other systemic therapy, **OR**
3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**
   a) Is being considered for anticancer therapy.

II. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.

back to top

KRAS Variant Analysis via ctDNA

I. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) is considered **medically necessary** when:

A. The member has metastatic colorectal cancer, **AND**

1. Testing for *NRAS* and *BRAF* is also being performed, either as separate tests or as part of an NGS panel, **OR**

B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**

1. Is being considered for anticancer therapy.

II. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.

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, unresectable, or stage IV hormone receptor-positive/HER2-negative breast cancer, **AND**

B. The member is considering treatment with alpelisib plus fulvestrant, or capivasertib plus fulvestrant, **AND**

C. The member has had progression on at least one line of therapy.

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

back to top

CIRCULATING TUMOR CELL TESTS

AR-V7 Circulating Tumor Cells (CTC) Analysis

I. AR-V7 circulating tumor cells (CTC) analysis (81479) is considered **medically necessary** when:
A. The member has a diagnosis of metastatic castration-resistant prostate cancer, **AND**
B. Tissue-based testing is not feasible for the member, **AND**
C. The test is ordered only once during the current cancer diagnosis, **AND**
D. The member has at least one of the following:
1. Newly metastatic cancer, **OR**
2. Signs of clinical, radiological or pathologic disease progression.

II. AR-V7 circulating tumor cells (CTC) analysis (81479) is considered **investigational** for all other indications.

back to top

Circulating Tumor Cell (CTC) Enumeration

I. Circulating Tumor Cell (CTC) enumeration (86152) is considered **investigational**.

back to top

DEFINITIONS

1. **Circulating tumor DNA (ctDNA):** 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.
2. **Circulating Tumor Cells (CTCs):** 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

PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

BACKGROUND AND RATIONALE

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

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer guidelines (4.2024) recommends evaluating tumor for mutations in homologous recombination DNA repair genes (such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*) in individuals with metastatic prostate cancer. In addition, MSI evaluation is recommended for metastatic prostate cancer. Plasma circulating tumor (ctDNA) assay is an option if biopsy is not able to be performed. (PROS-C, 2 of 2).

NCCN Gastric Cancer guidelines (2.2024) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management. NCCN recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced gastric cancer who may be unable to safely undergo a traditional biopsy. This testing can identify targetable mutations, clones with altered response profiles or monitor for disease progression. A negative result does not exclude the presence of tumor mutations or amplifications. (p. GAST-B 5 of 6)

NCCN Pancreatic Adenocarcinoma guidelines (3.2024) recommend tumor molecular profiling for patients with advanced or metastatic disease if anti-cancer treatment is being considered. While testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. PANC-1A) Of note, the recommendation for consideration of molecular testing is also included for any patient considering systemic therapy, at all stages of the disease including neoadjuvant therapy for resectable or borderline resectable disease. (p. PANC-1A)

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (4.2024) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management, NCCN recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced cancer whio may be unable to safely undergo a traditional biopsy. This testing can identify targetable mutations, clones with altered response profiles or monitor for disease progression. A negative result does not exclude the presence of tumor mutations or amplifications. (p. ESOPH-B 5 of 6)

NCCN Colon Cancer guidelines (4.2024) recommend broad molecular profiling for detection of mutations in RAS, BRAF and other genes along with HER2 amplifications and MSI, for patients with suspected or proven metastatic adenocarcinoma and can be done on tissue or blood. (p. COL-2). NCCN recommends consideration of repeat testing after targeted therapy to guide future treatment decisions. (p. COL-B, 4 of 10)

NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend broad-based biomarker testing using ctDNA only when disease is advanced or metastatic; tissue based testing is preferred for stage I-III disease. Both tissue and ctDNA testing have false negative rates and NCCN recommends consideration of complementary testing to increase the likelihood of mutation detection and reduce time to results. (p. NSCL-19, NSCL-H, 8 of 8)

NCCN Cutaneous Melanoma guidelines (2.2024) support the use of cell-free circulating tumor DNA (ctDNA) if tumor tissue is unavailable. (p. ME-C 3 of 8) *BRAF* mutation testing is recommended for patients with stage III disease who have a high likelihood of recurrence if future *BRAF*-directed therapy may be an option. *KIT* gene testing is recommended for stage IV or recurrent disease if

clinically appropriate. (p. ME-C, 4 of 8) Broader genomic profiling using larger NGS panels or full *BRAF* analysis is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If *BRAF* single-gene testing was already done and was negative, NCCN recommends consideration of larger NGS panels to identify other potential genetic targets. (p. ME-C 4 of 8)
NCCN Ampullary Adenocarcinoma guidelines (2.2024) recommend somatic molecular profiling for patients with locally advanced or metastatic disease when systemic therapy is being considered. Testing on tumor tissue is preferred but cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. AMP-6)
NCCN Cervical Cancer guidelines (3.2024) recommends consideration of comprehensive molecular profiling for cervical cancer that is persistent or recurrent after treatment. If biopsy of the metastatic site is not feasible or if no tissue is available, testing can be done on circulating tumor DNA. (p. CERV-11)
NCCN Biliary Tract Cancers guidelines (3.2024) recommend comprehensive molecular profiling for patients with unresectable or metastatic biliary tract cancer who are candidates for when systemic therapy is an option. NCCN recommends consideration of a cell-free DNA test if there is not enough tissue available or repeat biopsy cannot be done. (p. BIL-B, 1 of 8)
NCCN Histiocytic Neoplasms guidelines (2.2024) mention molecular testing in the workup for histiocytosis and state that if biopsy is not possible due to location or risk factors, mutational analysis of peripheral blood is an option (p. LCH-2, ECD-2, RDD-2)
NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) recommends consideration of t tumor molecular profiling for patients with locoregional unresectable/metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm when systemic therapy is being considered. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. PDNEC-1A)
NCCN Occult Primary guidelines (1.2025) recommend consideration of molecular profiling of tumor tissue after an initial determination of histology has been made. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. OCC-1A)
NCCN Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer guidelines (3.2024) recommend somatic testing for *BRCA1/2* and homologous recombination deficiency status for patients at diagnosis and broader molecular testing in the recurrence setting . especially for less common histologies with limited approved treatment options. Testing may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible. (p. OV-B, 1 of 3)
NCCN Breast Cancer guidelines (4.2024) recommend the use of comprehensive somatic profiling for patients with stage IV or recurrent invasive breast cancer to identify candidates for additional targeted therapies. Biomarker testing should be done on at least the first recurrence, and either tissue or plasma based assays can be used. (p. BINV-18)

Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
The NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend biomarker testing for *EGFR* mutations (among others) for patients with advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not otherwise specified. (p. NSCL-18). Tissue-based testing and ctDNA both have high specificity and false negative rates and therefore can be used together to reduce turnaround time and increase the likelihood of finding actionable targets. (p. NSCL-H, 8 of 8) In patients who have progressed following targeted therapy, NCCN recommends consideration of biomarker analysis to evaluate possible mechanisms of resistance. (p. NSCL-H, 7 of 8)

EGFR Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

The NCCN Non-Small Cell Lung Cancer guidelines (7.2024) recommend biomarker testing for *EGFR* mutations (among others) for patients with advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not otherwise specified. (p. NSCL-19) These guidelines also specify that ctDNA testing is not typically recommended for clinical settings except those in which the patient has advanced or metastatic disease. (p. NSCL-H 8 of 8)

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 (TKIs) 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 [cell-free DNA] assay to identify [activating] *EGFR* mutations." (p. 337)
- 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." (p. 337)
- 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." (p. 326)

BRAF Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (4.2024) recommend tumor molecular testing for *KRAS, NRAS*, and *BRAF* mutations in all patients with metastatic colorectal cancer. This analysis can be done either individually or as part of an NGS panel. Additionally, it is noted molecular testing can be performed on tissue as a preferred specimen type or blood-based assay. Finally, *KRAS, NRAS*, and *BRAF* mutation analysis can be performed on either primary colorectal tumors or on metastases. (p. COL-B, 4 of 10)

NCCN Cutaneous Melanoma guidelines (2.2024) recommend *BRAF* mutation testing for patients with cutaneous melanoma of at least stage III who are being considered for *BRAF* directed therapy or clinical trials. (p. ME-5A) Additionally, these guidelines state that molecular testing on tumor tissue is preferred, but may be performed on peripheral blood (liquid biopsy) if tumor tissue is not available. (p. ME-C 3 of 8)

NCCN Pancreatic Adenocarcinoma guidelines (3.2024) recommend tumor molecular profiling, including *BRAF*, for patients with advanced or metastatic disease who are candidates for systemic therapy. Tumor tissue is the preferred specimen for this testing, but cell-free DNA can be considered if testing on tissue is not feasible. (p. PANC-1A)

KRAS Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (4.2024) recommend tumor molecular testing for *KRAS, NRAS*, and *BRAF* mutations in all patients with metastatic colorectal cancer. This analysis can be done either individually or as part of an NGS panel. Additionally, it is noted molecular testing can be performed on tissue as a preferred specimen type or blood-based assay. Finally, *KRAS, NRAS*, and *BRAF*

mutation analysis can be performed on either primary colorectal tumors or on metastases. (p. COL-B, 4 of 10)
NCCN Pancreatic Adenocarcinoma guidelines (3.2024) recommend tumor molecular profiling, including *KRAS*, for patients with advanced or metastatic disease who are candidates for systemic therapy. Tumor tissue is the preferred specimen for this testing, but cell-free DNA can be considered if testing on tissue is not feasible (p. PANC-1A).

***PIK3CA* Variant Analysis via ctDNA**
National Comprehensive Cancer Network (NCCN)
NCCN Breast Cancer guidelines (4.2024) recommends *PIK3CA* mutation testing for patients with hormone receptor positive/HER2 negative recurrent unresectable or stage IV breast cancer to identify candidates for treatment with alpelisib or capivarsertib, plus fulvestrant, as a preferred second or subsequent line of therapy. Testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If the liquid biopsy is negative, tumor tissue testing is recommended. (p. BINV-Q, 6 of 14)

AR-V7 Circulating Tumor Cells (CTC) Analysis
Centers for Medicare and Medicaid Services
The CMS local coverage determination (LCD) entitled “MolDX: Phenotypic Biomarker Detection in Circulating Tumor Cells” includes the following coverage criteria for circulating tumor cells (CTCs):
“The evidence to date supports HER2 testing from CTCs in breast cancer and AR-V7 testing from CTCs in prostate cancer...In prostate cancer, the presence of AR-V7 from CTCs is currently the basis for making treatment decisions regarding taxane versus ARS inhibitor therapy…”.
The LCD continues on:
“Assays that detect biomarkers from CTCs are covered when ALL of the following are met:

- The specific cancer type has an associated biomarker
- At least 1 of the following criteria are met AND there is clear documentation of at least 1 of these in the medical record:
    - The patient’s cancer has not previously been tested for the specific biomarker, OR
    - The patient has newly metastatic cancer, and a metastatic lesion has not been tested for the specific biomarker, OR
    - The patient 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
- Tissue-based testing for the specific biomarker is infeasible (e.g., quantity not sufficient or invasive biopsy is medically contraindicated) OR will not provide sufficient information for subsequent medical management (e.g., 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.
- For a given patient 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.
- Duplicate testing of the same biomarker (from the same sample type and for the same clinical indication) using different methodologies is not covered. For example, testing for androgen receptor splice variant 7 (AR-V7) from CTCs by messenger RNA (mRNA) as well as immunohistochemistry (IHC)-based methodologies, for the same clinical indication, will not be covered.”

Circulating Tumor Cell (CTC) Enumeration Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Breast Cancer guidelines (4.2024) mention that guidance for clinical use of circulating tumor cells (CTC) in metastatic breast cancer assessment and monitoring is not currently part of the guideline. Studies mentioned showed that enumeration of circulating tumor cells did not have predictive value. (p. MS-75)
Centers for Medicare and Medicaid Services
In the CMS local coverage determination (LCD) "MolDX: Phenotype Biomarker Detection in Circulating Tumor Cells," the following is included regarding CTC enumeration analysis: "CTC enumeration may be a good prognostic indicator for certain cancers, but studies do not conclusively suggest a clear effect on outcomes resulting from a change in management."

back to top

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back to top

Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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