Revision log
Coding Implications

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

See Important Reminder at the end of this policy for important regulatory and legal information.

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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding 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.

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 Analysis via ctDNA	EGFR T790M Mutation Detection, Blood (University of Washington Medical Center - Laboratory Medicine-Genetics Laboratory)	81235	C34	1, 9
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 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 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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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee 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/enrollee 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.

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

   A. The member/enrollee 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.

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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 circulating tumor DNA (ctDNA) is considered **medically necessary** when:

   A. The member/enrollee 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.

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BRAF Variant Analysis via ctDNA

I. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) is considered **medically necessary** when**:**

A. The member/enrollee meets one of the following:

1. The member/enrollee 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/enrollee has stage III or higher cutaneous melanoma, **AND**

a) Is being considered for adjuvant or other systemic therapy, **OR**

3. The member/enrollee 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.

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KRAS Variant Analysis via ctDNA

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

A. The member/enrollee 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/enrollee 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.

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

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

C. The member/enrollee 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.

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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/enrollee has a diagnosis of metastatic castration-resistant prostate cancer, **AND**

   B. Tissue-based testing is not feasible for the member/enrollee, **AND**

   C. The test is ordered only once during the current cancer diagnosis, **AND**

   D. The member/enrollee 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.

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Circulating Tumor Cell (CTC) Enumeration

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

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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.

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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 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."

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table: replaced "Comprehensive" with "Broad"; under EGFR Variant Analysis via ctDNA: added "by Digital Droplet PCR"; under AR-V7	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs): removed "OncotypeDx"; removed "Exact"; added "Epic"; removed "Laboratories"; under Circulating Tumor Cell (CTC) Enumeration Analysis: removed "Count ARUP Laboratories"; added "University of Washington Medical Center". For Other Related Policies: added "and Molecular". For Criteria; Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA): in I., II. and III. replaced "Comprehensive" with "Broad"; I.A.11. added "Hormon receptor…"; for Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA): I.A. added "or progression"; for Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA): I.B. removed "KIT"; for Single Gene Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA): I.B. added "OR"; I.C. added "The testing is being done"; for BRAF Variant Analysis via ctDNA: I.A.2. removed "a diagnosis of cutaneous…"; I.A.2. added "stage"; I.A.4. removed "a diagnosis of pancreatic…"; I.A.3. added "locally"; I.B. replaced "At least" with "The member/enrollee meets"; for KRAS Variant Analysis via ctDNA: I.A. removed "and testing"; added "AND"; I.B. added "Testing"; removed "Pancreatic adenocarcinoma,,,"; I.C. removed "Has"; I.D. removed "At"; added "The member/enrollee meets"; for PIK3CA Cariant Analysis via ctDNA: removed "I.B. At least one of the following…"; added I.B. "The member/enrollee is considering…"; added I.C. "The member/enrollee has had progression…"; II. removed "as a stand alone test". For Background and Rationale: added "NCCN Breast Cancer guidelines…"; under Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA): added "state that broad…"; added "NCCN Non-Small Cell…"; under Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA): added "NCCN Non-Small Cell…"; under Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA): removed "BRAF mutation testing…"; added "The guidelines note…"; removed "disease and"; added "cutaneous melanoma"; removed "for whom future BRAF…"; added "or at stage IV…"; added "NCCN Non-Small Cell…"; under PIK3CA Variant Analysis via Circulating Tumor DNA (ctDNA): added "Assessing for POL3CA…".		
Added CPT codes 81462, 81463, and 81464 to the criteria for Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA).	11/23	
Semi-annual review. Updated title to reflect V2.2024 version. In Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA), minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA), clinical criteria removed due to lack of currently available tests for this indication. In Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA), minor clarification of criteria to update staging of cancer types to better align with guidelines, and removed additional tissue criteria to better align with guidelines. In Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA), clinical criteria removed due to lack of currently available tests for this indication. In *EGFR* Variant Analysis via ctDNA, updated criteria	04/24	04/24

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to align with current guidelines. Minor expansion via removal of requirement that tissue testing be unavailable, to align with updated guidelines. In *BRAF* Variant Analysis via ctDNA, updated criteria to align with current guidelines. Minor expansion via removal of requirement that tissue testing be unavailable, to align with updated guidelines In *KRAS* Variant Analysis via ctDNA, updated criteria to align with current guidelines. Minor expansion via removal of requirement that tissue testing be unavailable, to align with updated guidelines. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.		
Semi-annual review. Updated title to reflect V1.2025 version. Circulating Tumor Cell (CTC) Enumeration: Added new test entry for CELLSEARCH Circulating Melanoma Cell (0490U) in the Policy reference table; Added new test entry for CELLSEARCH ER Circulating Tumor Cell (0491U) in the Policy reference table; Added new test entry for CELLSEARCH PD-L1 Circulating Tumor Cell (0492U) in the Policy reference table; Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; Updated NCCN Breast Cancer guidelines from version 1.2024 to 2.2024; Removed the following tests and CPT codes from the Policy Reference Table and criteria; 1. CELLSEARCH HER2 Circulating Tumor Cell Test (Menarini Silicon Biosystems) - 0338U, 2. CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test (Menarini Silicon Biosystems) - 0337U, 3. Circulating Tumor Cells for Colorectal Cancer by CellSearch (University of Michigan - Michigan Medical Genetics Laboratories) - 86152, 86153; Added the CELLSEARCH Circulating Tumor Cell (CTC) Test (CELLSEARCH) test with CPT code 86152 to the policy reference table; Added the following statements to the Background and Rationale; 1. "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)"; 2. "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.”"; New reference added "Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Phenotypic Biomarker Detection in Circulating Tumor Cells (L38566) Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38566". AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs): Removed specific criteria set due to low volume and removal of recommendation from NCCN; Indication would not fall under the General Policy. KRAS Variant Analysis via ctDNA: Updated NCCN versions in Background and Rationale and references; Removed NCCN guideline for lung cancer from Background and Rationale as lung cancer is not in the coverage criteria. BRAF Variant Analysis via ctDNA: Updated NCCN versions in Background and Rationale and references; Removed	11/24	11/24

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NCCN guideline for lung cancer from Background and Rationale as lung cancer is not in the coverage criteria. Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA): Added criterion to allow concurrent ctDNA and solid tumor tissue testing for advanced or metastatic non-small cell lung cancer; Added new test entry for Caris Assure (0485U) in the Policy reference table; Added new test entry for Northstar Select (0487U) in the Policy reference table; Added new test entry for OptiSeq Dual Cancer Panel Kit (0499U) in the Policy reference table; Removed the term "extrapulmonary poorly" in criteria to simplify criteria for medical review; Updated NCCN versions in Background and Rationale and references. PIK3CA Variant Analysis via ctDNA: Added second drug (capivasertib) for treatment consideration to allow coverage for testing; Updated tests in Policy Reference Table, updated NCCN versions in Background and Rationale and references. Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA): Reworded criteria to say "advanced" lung cancer rather than stage IV to be consistent with NCCN; NCCN versions updated in Background and Rationale and references. EGFR Variant Analysis via ctDNA: Limited coverage for testing to patients with advanced or metastatic disease to align with NCCN guidelines; Reworded criteria to say "advanced" lung cancer rather than stage IV to be consistent with NCCN; Removed reference, updated NCCN versions in Background and Rationale and references. AR-V7 Circulating Tumor Cells (CTC) Analysis: NEW criteria set developed based on LCD guideline.		

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to

recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, member/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

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