CONCERT GENETICS 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) 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

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

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

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, C18, C25, C34, C61	1, 2, 3, 4, 6, 7, 8
	Guardant360® CDx (Guardant Health)	0242U		
	Guardant360® 83+ genes (Guardant Health)	0326U		
	NeoLAB® Solid Tumor Liquid Biopsy (NeoGenomics Laboratories)	81445		
	Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus)	81455		
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 (Inivata)	81445		
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 through C21	3
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	C34	1, 10, 11
	EGFR T790M Mutation Detection in			

	ctDNA (ARUP Laboratories)			
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600 Test (Mayo Medical Laboratories)	81210	C18 through 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 through C20	3, 9
PIK3CA Variant Analysis via ctDNA	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	0177U	C50	5
	PIK3CA Mutation CDx - Plasma (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 Cell Count (ARUP Laboratories)	86152, 86153	C00.0 through C96.9	5

OTHER RELATED POLICIES

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

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.
- ***Oncology*: *Algorithmic Testing*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.

- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to circulating tumor DNA or circulating tumor cell testing that is not specifically discussed in this or another non-general policy.

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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)

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, 81445, 81455) are considered **medically necessary** when:

A. The member/enrollee has a diagnosis, progression, or recurrence 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. Advanced (stage III or higher) cutaneous melanoma**, OR**
10. Metastatic colorectal cancer, **AND**

B. At least one of the following:

1. The member/enrollee 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. Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455) are considered **investigational** for all other indications.

III. Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455) performed simultaneously with solid tumor tissue testing are considered **investigational**.

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

I. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81275, 81479, 81445) are considered **medically necessary** when:

A. The member/enrollee 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. At least one of the following:

1. The member/enrollee 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, 81275, 81479, 81445) are considered **investigational** for all other indications.

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

I. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81311, 81403, 81479) are considered **medically necessary** when:

A. Member/enrollee has metastatic colorectal adenocarcinoma, **AND**

B. Panel includes *KRAS*, *NRAS*, and *BRAF* analysis, **AND**

C. At least one of the following:

1. The member/enrollee 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. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81311, 81403, 81479) are considered **investigational** for all other indications.

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Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)

I. Melanoma focused panel tests via circulating tumor DNA (ctDNA) (81210, 81311, 81479) are considered medically necessary when:

   A. Member/enrollee has advanced (stage III or higher) cutaneous melanoma, **AND**

   B. Panel includes *BRAF*, *NRAS*, and *KIT*, **AND**

   C. At least one of the following:

      1. The member/enrollee 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. Melanoma focused panel tests via circulating tumor DNA (ctDNA) (81210, 81311, 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 cell-free circulating tumor DNA (ctDNA) is considered **medically necessary** when:

   A. The member/enrollee 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/enrollee 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) via cell-free circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational** for all other indications.

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BRAF Variant Analysis via ctDNA

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

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

1. The member/enrollee has metastatic colorectal cancer and testing for *NRAS* and KRAS is also being performed, either as separate tests or as part of an NGS panel, **OR**

2. The member/enrollee has a diagnosis of cutaneous melanoma and meets all of the following:

a) Stage III or higher cutaneous melanoma, **AND**

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

3. The member/enrollee has a diagnosis of pancreatic adenocarcinoma and meets all of the following:

a) Locally advanced or metastatic pancreatic adenocarcinoma, **AND**

b) Is being considered for anticancer therapy, **AND**

B. At least one of the following:

1. The member/enrollee 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. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) for advanced or metastatic non-small cell lung cancer, when not part of a larger molecular profiling panel, is considered **investigational**.

III. *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 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 pancreatic adenocarcinoma and meets all of the following:

1. Has locally advanced or metastatic pancreatic adenocarcinoma, **AND**

2. Is being considered for anticancer therapy, **AND**

C. At least one of the following:

1. The member/enrollee 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. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) for advanced or metastatic non-small cell lung cancer when not part of a larger molecular profiling panel is considered **investigational**.

III. *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. At least one of the following:

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

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CIRCULATING TUMOR CELL TESTS

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

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

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

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

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

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Circulating Tumor Cell (CTC) Enumeration

I. Circulating Tumor Cell (CTC) enumeration (86152, 86153) is considered **investigational**.

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NOTES AND DEFINITIONS

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

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

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CLINICAL CONSIDERATIONS

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

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

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

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BACKGROUND AND RATIONALE

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

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer guidelines (1.2023) recommends evaluating tumor for alterations in homologous recombination DNA repair genes (such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12) in individuals with metastatic prostate cancer. When unsafe or unfeasible, plasma circulating tumor (ctDNA) assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield. Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. (p. PROS-C 3 of 3)

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 clones with altered treatment response profiles. Patients who have metastatic or advanced gastric cancer who may be unable to undergo a traditional biopsy for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications. (p. GAST-B 5 of 6)

NCCN Pancreatic Adenocarcinoma guidelines (2.2022) state that while testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible. This testing should be performed for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy (p. PANC-1A). Of note, the recommendation for molecular testing was included in all disease categories (i.e. clinical presentation, locally advanced, metastatic, disease progression and recurrence).

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (5.2022) 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 the DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clone with altered treatment response profiles. Patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications. (p. ESOPH-B 5 of 6).

NCCN Colon Cancer guidelines (3.2022) state that *RAS* and *BRAF* mutation analysis and HER2 amplification can be tested by individual genes or as part of a next generation sequencing panel, either by tissue or blood-based assay. (p. COL-4) Guidelines also state that determination of tumor gene status for RAS and BRAF mutations (individually or as part of tissue or blood-based NGS panel) is recommended for recurrent colon cancer. (p. COL-9).

NCCN Non-Small Cell Lung Cancer guidelines (2.2023) support the use of cell-free circulating tumor DNA (ctDNA) testing if a patient is not medically fit for invasive tissue sampling, if there is insufficient tissue for molecular analysis, or if the available tissue is unable to undergo all recommended genetic testing due to tissue sufficiency or available testing methodologies. If ctDNA testing is negative, there should be follow-up tissue-based analysis. NCCN recognizes studies have shown a high sensitivity, but a significantly compromised sensitivity, with up to 30% false-negative rate. This does not support the use of ctDNA testing in lieu of a histologic tissue diagnosis, when it is possible and feasible (p. NSCL-H 7 of 7).

NCCN Cutaneous Melanoma guidelines (1.2023) 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 at high risk for recurrence for whom future *BRAF*-directed therapy may be an option. For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g,, larger NGS panels, *BRAF* non-V600 mutations) 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 the initial test

performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT and BRAF* non-V600). (p. ME-C 4 of 8)

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

National Comprehensive Cancer Network (NCCN)

The NCCN Non-Small Cell Lung Cancer guidelines (2.2023) 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. (page NSCL-18)

NCCN Non-Small Cell Lung Cancer guidelines (2.2023) support the use of cell-free circulating tumor DNA (ctDNA) testing if a patient is either not medically fit for invasive tissue sampling, if the tissue available is not able to undergo testing for all recommended biomarkers due to tissue quantity or available testing technologies, 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 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, when 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 (3.2022) state that for patients with metastatic colorectal adenocarcinoma tumor testing should be done for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. This testing can be done as part of a panel or individually, and can be done on formalin-fixed, paraffin-embedded (FFPE) tissue or blood-based testing (p. COL-B 4 of 8)

Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

NCCN Cutaneous Melanoma guidelines (1.2023) state molecular testing may be performed on tumor tissue, or if not available, on peripheral blood (liquid biopsy). (p. ME-C 3 of 8)

BRAF mutation testing is recommended for patients with stage III disease and at high risk for recurrence for whom future *BRAF*-directed therapy may be an option. For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g., larger NGS panels, *BRAF* non-V600 mutations) 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 the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT and BRAF* non-V600). (p. ME-C 4 of 8)

EGFR Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

The NCCN Non-Small Cell Lung Cancer guidelines (2.2023) 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. (page NSCL-18)

The NCCN Non-Small Cell Lung Cancer guidelines (2.2023) state that the use of cfDNA tumor testing “can be considered” in specific clinical situations including:

- A patient is not medically fit for invasive tissue sampling
- If there is not sufficient tumor material for molecular analysis and an oncogenic driver mutation has not previously been identified, and/or if tissue-based testing is performed but did not completely assess all recommended biomarkers due to tissue quantity and/or availability of testing methodologies. (page NSCL-H 7 of 7)

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." (Page 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." (Page 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." (Page 326)

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 the 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." (First paragraph of statement)

BRAF Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (3.2022) state all patients with metastatic colorectal cancer should have tumor genotyped for KRAS, NRAS, and BRAF mutations. 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 8)

NCCN Cutaneous Melanoma guidelines (1.2023) state for patients with cutaneous melanoma of at least stage III or higher and who are being considered for adjuvant therapy or clinical trial, BRAF mutation testing is a part of the recommended workup (p. ME-4, ME-4A, 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 (2.2022) state that tumor molecular profiling is recommended for patients with advanced or metastatic disease who are candidates for anti-cancer therapy. They suggest including the following genes that have known mutations that have actionable findings: BRAF, BRCA1/2, KRAS, PALB2. They indicate that 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).

NCCN Non-Small Cell Lung Cancer guidelines (2.2023) strongly advises broad molecular profiling for advanced or metastatic disease (p. NSCL-18). They define broad molecular profiling as molecular testing for their recommended biomarkers (EGFR, KRAS, ALK rearrangements, ROS1 rearrangements, NTRK1/2/3 gene fusions, BRAF V600E, METex14 skipping, RET rearrangements, ERBB2/HER2, and PDL-1) as well as emerging biomarkers, either in a single assay or a limited number of assays (p. NSCL-18, NSCL-19). NCCN also states that in situations where tissue is minimal, peripheral blood (plasma circulating tumor DNA) can be a surrogate sample for tumor tissue (p. NSCL-H 1 of 7).

KRAS Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (3.2022) state that all patients with metastatic colorectal cancer should have tumor genotyped for KRAS, NRAS, and BRAF mutations. This analysis can be done either individually or as part of an NGS panel. Additionally, it is noted that 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 8).

NCCN Pancreatic Adenocarcinoma guidelines (2.2022) state tumor molecular profiling is recommended for patients with advanced or metastatic disease who are candidates for anti-cancer therapy. They suggest including the following genes that have known mutations that have actionable findings: BRAF, BRCA1/2, KRAS, and PALB2. They indicate 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).

NCCN Non-Small Cell Lung Cancer Guidelines (2.2023) strongly advise broad molecular profiling for advanced or metastatic disease (p. NSCL-18). They define broad molecular profiling as molecular testing for their recommended biomarkers (EGFR, KRAS, ALK rearrangements, ROS1 rearrangements, NTRK1/2/3 gene fusions, BRAF V600E, METex14 skipping, RET rearrangements, ERBB2/HER2, and PDL-1) as well as emerging biomarkers, either in a single assay or a limited number of assays (p. NSCL-18, NSCL-19). NCCN also states in situations where tissue is minimal, peripheral blood (plasma circulating tumor DNA) can be a surrogate sample for tumor tissue (p. NSCL-H 1 of 7).

PIK3CA Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (2.2023) states patients with hormone receptor positive/HER2 negative breast cancer, ***PIK3CA*** mutation 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-R 1 of 3).

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

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer guidelines (1.2023) 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

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (2.2023) recognize 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).

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	03/23	03/23

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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 members/enrollees. This clinical policy is not intended to

recommend treatment for members/enrollees. Members/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, members/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, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/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 members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, 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.