BSC_CON_2.10	Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)		
Original Policy Date:	June 1, 2023	**Effective Date:**	July 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 20

Example Test Table

The tests and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
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
	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)	
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung (Labcorp)	0179U
	OncoBEAM Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc.)	81210, 81235, 81275, 81479
	InVisionFirst-Lung Liquid Biopsy (Inivata)	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
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600, Blood (Mayo Medical Laboratories)	81210
	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
PIK3CA Variant Analysis via ctDNA	therascreen PIK3CA RGQ PCR Kit (QIAGEN)	0177U
	PIK3CA Mutation CDx - Plasma (NeoGenomics Laboratories)	81309
Circulating Tumor Cell (CTC) Tests		

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)	AR-V7 Nucleus Detect (Epic Sciences)	81479
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH HER2 Circulating Tumor Cell Test (Menarini Silicon Biosystems)	0338U
	CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test (Menarini Silicon Biosystems)	0337U
	Circulating Tumor Cells for Colorectal Cancer by CellSearch (University of Michigan - Michigan Medical Genetics Laboratories)	86152, 86153

Policy Statement

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) may be 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
      2. Stage IV or metastatic large cell lung carcinoma
      3. Stage IV or metastatic squamous cell lung carcinoma
      4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
      5. Locally advanced/metastatic pancreatic adenocarcinoma
      6. Metastatic or advanced gastric cancer
      7. Metastatic or advanced esophageal or esophagogastric junction cancer
      8. Metastatic prostate cancer
      9. Stage III or higher cutaneous melanoma
      10. Metastatic colorectal cancer
      11. Locally advanced or metastatic ampullary adenocarcinoma
      12. Persistent or recurrent cervical cancer
      13. Unresectable or metastatic biliary tract cancer
      14. Suspected or confirmed histiocytic neoplasm
      15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma or large or small cell carcinoma or mixed neuroendocrine-non-neuroendocrine neoplasm
      16. Suspected metastatic malignancy of unknown primary with initial determination of histology
      17. Recurrent ovarian, fallopian tube or primary peritoneal cancer
      18. Recurrent or stage IV breast cancer.

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.

III. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455, 81462, 81463, 81464) performed simultaneously with solid tumor tissue testing are considered **investigational**.

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

IV. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81275, 81462, 81479, 0388U) may be considered **medically necessary** when:
   A. The member has a diagnosis or progression of **any** of the following:
      1. Stage IV or metastatic lung adenocarcinoma
      2. Stage IV or metastatic large cell lung carcinoma
      3. Stage IV or metastatic squamous cell lung carcinoma
      4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

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

Single Gene Molecular Profiling Panel Tests Via Circulating Tumor DNA (ctDNA)

EGFR Variant Analysis via ctDNA

VI. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **both** of the following are met:
   A. The member has a diagnosis of **any** of the following:
      1. Stage IB to IIIA or IIIB or metastatic lung adenocarcinoma
      2. Stage IB to IIIA or IIIB or metastatic large cell lung carcinoma
      3. Stage IB to IIIA or IIIB or metastatic squamous cell lung carcinoma
      4. Stage IB to IIIA or IIIB or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
   B. Treatment with an *EGFR* tyrosine kinase inhibitor therapy (examples: erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) is being considered.

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

BRAF Variant Analysis via ctDNA

VIII. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) may be 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
      2. The member has stage III or higher cutaneous melanoma, **AND**
         a. Is being considered for adjuvant or other systemic therapy
      3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**
         a. Is being considered for anticancer therapy.

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

KRAS Variant Analysis via ctDNA

X. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **either** of the following are met:
   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
   B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**
      1. Is being considered for anticancer therapy.

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

PIK3CA Variant Analysis via ctDNA

XII. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **all** of the following are met:
   A. The member has recurrent, unresectable, or stage IV hormone receptor-positive/HER2-negative breast cancer
   B. The member is considering treatment with alpelisib plus fulvestrant
   C. The member has had progression on at least one line of therapy.

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

Circulating Tumor Cell Tests

AR-V7 Circulating Tumor Cells (CTC) Analysis

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

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

Circulating Tumor Cell (CTC) Enumeration

XVI. Circulating Tumor Cell (CTC) enumeration (0337U, 0338U, 86152, 86153) is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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.

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.

Coding
See the Codes table for details.

Description

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.

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.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker

test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Rationale

Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
NCCN Prostate Cancer guidelines (4.2023) 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 (3.2023) 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 (1.2024) 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 (4.2023) 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 (1.2024) 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 (2.2024) recommend biomarker testing for stage IVA NSCLC (p. NSCL-13). 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 (3.2023) 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, and broader genomic profiling can be considered if the test results might guide further treatment decisions or eligibility for participation in a clinical trial (p. ME-5, 5A). 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)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend somatic molecular profiling for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy. 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 guidelines for Cervical Cancer (1.2024) indicate that comprehensive molecular profiling should be considered for cervical cancer that is persistent or recurrent after treatment and if tissue biopsy of the metastatic site is not feasible or tissue is not available, a ctDNA assay can be used. (p. CERV-11).
NCCN Biliary Tract Cancers guidelines (3.2023) recommend comprehensive molecular profiling for patients with unresectable or metastatic biliary tract cancer who are candidates for systemic therapy. A cell-free DNA test may be considered for identifying mutations but may not reliably identify gene fusions or rearrangements depending on the panel used and the specific partner gene. (p. BIL-B, 1 of 8)

NCCN guidelines for Histiocytic Neoplasms (1.2023) 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 guidelines for Neuroendocrine and Adrenal Tumors (1.2023) state that tumor profiling should be considered for patients with locoregional unresectable/metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm who are candidates for anti-cancer therapy to identify actionable alterations. 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 guidelines for Occult Primary (1.2024) state that molecular profiling of tumor tissue using next-generation sequencing (or other technique to identify gene fusions) can be considered 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. OCC1-1A)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (1.2024) state that tumor molecular analysis in the recurrence setting should include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit. These include (but are not limited to): *BRCA1/2*, HR status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), *BRAF*, and *NTRK*, if prior testing did not include these markers. More comprehensive tumor analysis may be particularly important for less common histologies with limited approved treatment options. Molecular analyses 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 (1.2024) support 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 (2.2024) 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). If ctDNA testing is negative, there should be follow-up with tissue-based analysis. NCCN recognizes studies have shown generally high specificity, but a significantly compromised sensitivity with up to 30% false-negative rate ; however data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection. (p. NSCL-H 7 of 7).

NCCN Non-Small Cell Lung Cancer guidelines (2.2024) state that broad molecular testing (either blood-based or tissue-based) should be considered at time of progression. (p. NSCL-22)

EGFR Variant Analysis via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
The NCCN Non-Small Cell Lung Cancer guidelines (2.2024) recommend biomarker testing for *EGFR* mutations (among others) for patients with stage IB to IIIA and stage IIIB disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not otherwise specified. (p. NSCL-H, 3 of 7, NSCL-18)

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)

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 (1.2024) 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 (3.2023) 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 (1.2024) 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 (2.2024) 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 (1.2024) 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 (1.2024) 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 (2.2024) 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 (1.2024) states that for 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. Assessing for *PIK3CA* mutations in patients with hormone receptor positive/HER2 negative breast cancer is recommended to identify candidates for therapy via alpelisib plus fulvestrant. It is also recommended that these agents be used as a preferred second- or subsequent-line therapy (p. BINV-Q 6 of 14).

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

National Comprehensive Cancer Network (NCCN)
NCCN Prostate Cancer guidelines (4.2023) 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 (1.2024) 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).

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."

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 4.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 4.2023 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
8. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
9. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP
10. Cobas EGFR Mutation Test v2. U.S. Food & Drug Administration website. Published June 2, 2016. Accessed July 1, 2021. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/cobas-egfr-mutation-test-v2

11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms. Version 1.2023 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary [CUP]). Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
18. 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

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
	0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
	0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
	0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood
	0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
	0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
	81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
	81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for

Type	Code	Description
		sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements ***(Code effective 1/1/2024)***
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability ***(Code effective 1/1/2024)***
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	81479	Unlisted molecular pathology procedure
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood);
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2023	New policy (combined policies 2.04.141 and 2.04.45).
07/01/2023	Administrative update. Coding update.
11/01/2023	Administrative update. Coding update.
03/01/2024	Coding update.
07/01/2024	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent

therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) BSC_CON_2.10 **Policy Statement:** I. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) may be considered **medically necessary** at diagnosis progression or recurrence when **BOTH** of the following criteria are met: A. The member has a diagnosis of **ONE** of the following: 1. Non-small cell lung cancer (e.g., adenocarcinoma, large cell carcinoma, squamous cell carcinoma, not otherwise specified) must include EGFR 2. Locally advanced/metastatic pancreatic adenocarcinoma 3. Gastric cancer 4. Esophageal or esophagogastric junction cancer 5. Metastatic prostate cancer (must include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; 0239U meets, 0242U and 0326U do not meet) 6. Metastatic colorectal cancer (must include *KRAS, NRAS* and *BRAF)* 7. Advanced or metastatic breast cancer when *PIK3CA* and *ESR1* is included in the panel for hormone receptor-positive, *HER2* negative individuals B. At least **ONE** of the following:	**Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) BSC_CON_2.10** **Policy Statement:** **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) may be 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 2. Stage IV or metastatic large cell lung carcinoma 3. Stage IV or metastatic squamous cell lung carcinoma 4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS) 5. Locally advanced/metastatic pancreatic adenocarcinoma 6. Metastatic or advanced gastric cancer 7. Metastatic or advanced esophageal or esophagogastric junction cancer 8. Metastatic prostate cancer 9. Stage III or higher cutaneous melanoma 10. Metastatic colorectal cancer 11. Locally advanced or metastatic ampullary adenocarcinoma 12. Persistent or recurrent cervical cancer 13. Unresectable or metastatic biliary tract cancer 14. Suspected or confirmed histiocytic neoplasm 15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma or large or

POLICY STATEMENT	
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1. The member is medically unfit for invasive tissue sampling (biopsy) 2. Biopsy was performed but material was insufficient for complete molecular analysis	small cell carcinoma or mixed neuroendocrine-non-neuroendocrine neoplasm 16. Suspected metastatic malignancy of unknown primary with initial determination of histology 17. Recurrent ovarian, fallopian tube or primary peritoneal cancer 18. Recurrent or stage IV breast cancer.
II. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) are considered **investigational** for all other indications.	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.
III. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) performed simultaneously with solid tumor tissue testing is considered **investigational**.	III. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455, 81462, 81463, 81464) performed simultaneously with solid tumor tissue testing are considered **investigational**. **Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)** IV. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81275, 81462, 81479, 0388U) may be considered **medically necessary** when: A. The member has a diagnosis or progression of **any** of the following: 1. Stage IV or metastatic lung adenocarcinoma 2. Stage IV or metastatic large cell lung carcinoma 3. Stage IV or metastatic squamous cell lung carcinoma 4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS). V. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81275, 81462, 81479, 0388U) are considered **investigational** for all other indications. **Single Gene Molecular Profiling Panel Tests Via Circulating Tumor DNA (ctDNA)** ***EGFR* Variant Analysis via ctDNA**

POLICY STATEMENT	
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	VI. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of **any** of the following: 1. Stage IB to IIIA or IIIB or metastatic lung adenocarcinoma 2. Stage IB to IIIA or IIIB or metastatic large cell lung carcinoma 3. Stage IB to IIIA or IIIB or metastatic squamous cell lung carcinoma 4. Stage IB to IIIA or IIIB or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS) B. Treatment with an *EGFR* tyrosine kinase inhibitor therapy (examples: erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) is being considered. VII. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational** for all other indications. ***BRAF* Variant Analysis via ctDNA** VIII. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) may be 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 2. The member has stage III or higher cutaneous melanoma, **AND** a. Is being considered for adjuvant or other systemic therapy 3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** a. Is being considered for anticancer therapy. IX. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.

POLICY STATEMENT	
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	***KRAS* Variant Analysis via ctDNA** X. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **either** of the following are met: 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 B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** 1. Is being considered for anticancer therapy. XI. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications. ***PIK3CA* Variant Analysis via ctDNA** XII. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA) may be considered **medically necessary** when **all** of the following are met: A. The member has recurrent, unresectable, or stage IV hormone receptor-positive/HER2-negative breast cancer B. The member is considering treatment with alpelisib plus fulvestrant C. The member has had progression on at least one line of therapy. XIII. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA), is considered **investigational** for all other indications. **CIRCULATING TUMOR CELL TESTS** **AR-V7 Circulating Tumor Cells (CTC) Analysis** XIV. AR-V7 circulating tumor cells (CTC) analysis (81479) may be considered **medically necessary** when **all** of the following are met: A. The member has a diagnosis of metastatic castration-resistant prostate cancer B. Tissue-based testing is not feasible for the member
IV. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member has metastatic castration-resistant prostate cancer (M1 CRPC)	

POLICY STATEMENT	
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B. The member has had a progression after first-line treatment with enzalutamide (Xtandi®) or abiraterone (Zytiga®). V. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **investigational** for all other indications. VI. Circulating tumor cell (CTC) enumeration (86152, 86153) is considered **investigational**.	C. The test is ordered only once during the current cancer diagnosis D. The member has at least **one** of the following: 1. Newly metastatic cancer 2. Signs of clinical, radiological or pathologic disease progression. XV. AR-V7 circulating tumor cells (CTC) analysis (81479) is considered **investigational** for all other indications. **Circulating Tumor Cell (CTC) Enumeration** XVI. Circulating Tumor Cell (CTC) enumeration (0337U, 0338U, 86152, 86153) is considered **investigational**.