BSC_CON_2.10	Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 20

Example Test Table

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

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 (NeoGenomics)	0388U
	GeneStrat NGS (Biodesix)	81462
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)		
EGFR Variant Analysis via ctDNA	EGFR T790M Mutation Detection, Blood (University of Washington Medical Center - Laboratory Medicine-Genetics Laboratory)	81235
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
	Cell-Free DNA PIK3CA Test, Blood (Mayo Medical Laboratories)	81309
Circulating Tumor Cell (CTC) Tests		

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
AR-V7 Circulating Tumor Cells (CTC) Analysis	AR-V7 Circulating Tumor Cells (CTC) Analysis	81479
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH Circulating Tumor Cell (CTC) Test (CELLSEARCH)	86152
	CELLSEARCH Circulating Melanoma Cell (CMC) Test (Menarini Silicon)	0490U
	CELLSEARCH ER Circulating Tumor Cell (CTC-ER) Test (Menarini Silicon)	0491U
	CELLSEARCH PD-L1 Circulating Tumor Cell (CTC-PDL1) Test (Menarini Silicon)	0492U

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, **OR**
      2. Stage IV or metastatic large cell lung carcinoma, **OR**
      3. Stage IV or metastatic squamous cell lung carcinoma, **OR**
      4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
      5. Locally advanced or metastatic pancreatic adenocarcinoma, **OR**
      6. Metastatic or advanced gastric cancer, **OR**
      7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**
      8. Metastatic prostate cancer, **OR**
      9. Stage III or higher cutaneous melanoma**, OR**
      10. Metastatic colorectal cancer, **OR**
      11. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
      12. Persistent or recurrent cervical cancer**, OR**
      13. Unresectable or metastatic biliary tract cancer**, OR**
      14. Suspected or confirmed histiocytic neoplasm, **OR**
      15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR**
      16. Locoregional unresectable or metastatic large or small cell carcinoma, **OR**
      17. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm**, OR**
      18. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**
      19. Recurrent ovarian, fallopian tube or primary peritoneal cancer**, OR**
      20. Recurrent or stage IV breast cancer, **AND**
   B. If a broad molecular profiling panel test via circulating tumor DNA is being performed simultaneously with solid tumor tissue testing, the member must have one of the following diagnoses:
      1. Lung adenocarcinoma, **OR**
      2. Large cell lung carcinoma, **OR**
      3. Squamous cell lung carcinoma, **OR**
      4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

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

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

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

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

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

***EGFR* Variant Analysis via ctDNA**

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

VI. *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**

VII. *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, **OR**
      2. The member has stage III or higher cutaneous melanoma, **AND**
         a. Is being considered for adjuvant or other systemic therapy, **OR**
      3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**
         a. Is being considered for anticancer therapy.

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

***KRAS* Variant Analysis via ctDNA**

IX. *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, **OR**

B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND**
   1. Is being considered for anticancer therapy.

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

PIK3CA Variant Analysis via ctDNA

XI. *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, **AND**
   B. The member is considering treatment with alpelisib plus fulvestrant, or capivasertib plus fulvestrant, **AND**
   C. The member has had progression on at least one line of therapy.

XII. *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

XIII. 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, **AND**
   B. Tissue-based testing is not feasible for the member, **AND**
   C. The test is ordered only once during the current cancer diagnosis, **AND**
   D. The member has at least **one** of the following:
      1. Newly metastatic cancer, **OR**
      2. Signs of clinical, radiological or pathologic disease progression.

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

Circulating Tumor Cell (CTC) Enumeration

Circulating Tumor Cell (CTC) enumeration (86152) 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.

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.

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

Cell-free circulating tumor DNA analysis should not be performed simultaneously with tissue testing of a solid tumor, with the exception of lung cancer.

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

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

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

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

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

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

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

NCCN Cutaneous Melanoma guidelines (2.2024) support the use of cell-free circulating tumor DNA (ctDNA) if tumor tissue is unavailable. (p. ME-C 3 of 8) *BRAF* mutation testing is recommended for patients with stage III disease who have a high likelihood of recurrence if future *BRAF*-directed therapy may be an option. *KIT* gene testing is recommended for stage IV or recurrent disease if clinically appropriate. (p. ME-C, 4 of 8) Broader genomic profiling using larger NGS panels or full *BRAF* analysis is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If *BRAF* single-gene testing was already done and was negative, NCCN recommends consideration of larger NGS panels to identify other potential genetic targets. (p. ME-C 4 of 8)

NCCN Ampullary Adenocarcinoma guidelines (2.2024) recommend somatic molecular profiling for patients with locally advanced or metastatic disease when systemic therapy is being considered. Testing on tumor tissue is preferred but cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. AMP-6)

NCCN Cervical Cancer guidelines (3.2024) recommends consideration of comprehensive molecular profiling for cervical cancer that is persistent or recurrent after treatment. If biopsy of the metastatic site is not feasible or if no tissue is available, testing can be done on circulating tumor DNA. (p. CERV-11)

NCCN Biliary Tract Cancers guidelines (3.2024) recommend comprehensive molecular profiling for patients with unresectable or metastatic biliary tract cancer who are candidates for when systemic therapy is an option. NCCN recommends consideration of a cell-free DNA test if there is not enough tissue available or repeat biopsy cannot be done. (p. BIL-B, 1 of 8)

NCCN Histiocytic Neoplasms guidelines (2.2024) mention molecular testing in the workup for histiocytosis and state that if biopsy is not possible due to location or risk factors, mutational analysis of peripheral blood is an option (p. LCH-2, ECD-2, RDD-2)

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) recommends consideration of t tumor molecular profiling for patients with locoregional unresectable/metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm when systemic therapy is being considered. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. PDNEC-1A)

NCCN Occult Primary guidelines (1.2025) recommend consideration of molecular profiling of tumor tissue after an initial determination of histology has been made. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. OCC-1A) NCCN Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer guidelines (3.2024) recommend somatic testing for *BRCA1/2* and homologous recombination deficiency status for patients at diagnosis and broader molecular testing in the recurrence setting . especially for less

common histologies with limited approved treatment options. Testing may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible. (p. OV-B, 1 of 3)

NCCN Breast Cancer guidelines (4.2024) recommend the use of comprehensive somatic profiling for patients with stage IV or recurrent invasive breast cancer to identify candidates for additional targeted therapies. Biomarker testing should be done on at least the first recurrence, and either tissue or plasma based assays can be used. (p. BINV-18)

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

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

EGFR Variant Analysis via ctDNA

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

College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology
The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (2018) published a guideline on molecular testing for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors (TKIs) and noted the following recommendations regarding liquid biopsy for activating *EGFR* mutations and a consensus opinion regarding liquid biopsy for the T790M resistance mutation:

- Recommendation: "In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA [cell-free DNA] assay to identify [activating] *EGFR* mutations." (p. 337)
- Expert Consensus Opinion: "Physicians may use plasma cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to *EGFR* targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative." (p. 337)
- No recommendation: "There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of *EGFR* TKI resistance." (p. 326)

BRAF Variant Analysis via ctDNA

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

mutation analysis can be performed on either primary colorectal tumors or on metastases. (p. COL-B, 4 of 10)

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

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

KRAS Variant Analysis via ctDNA

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

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

PIK3CA Variant Analysis via ctDNA

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

AR-V7 Circulating Tumor Cells (CTC) Analysis

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

- The specific cancer type has an associated biomarker
- At least 1 of the following criteria are met AND there is clear documentation of at least 1 of these in the medical record:
    - The patient's cancer has not previously been tested for the specific biomarker, OR
    - The patient has newly metastatic cancer, and a metastatic lesion has not been tested for the specific biomarker, OR
    - The patient demonstrates signs of clinical, radiological or pathologic disease progression, OR

    - There is concern for resistance to treatment based on specific and well-established clinical indications
- Tissue-based testing for the specific biomarker is infeasible (e.g., quantity not sufficient or invasive biopsy is medically contraindicated) OR will not provide sufficient information for subsequent medical management (e.g., in cases where human epidermal growth factor receptor 2 (HER2) overexpression is negative in a tissue biopsy but may be positive in the CTCs, due to tumor heterogeneity). There is clear documentation of at least 1 of these reasons for testing in the medical record.
- For a given patient encounter, only 1 test for assessing the biomarker may be performed UNLESS a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test.
- Duplicate testing of the same biomarker (from the same sample type and for the same clinical indication) using different methodologies is not covered. For example, testing for androgen receptor splice variant 7 (AR-V7) from CTCs by messenger RNA (mRNA) as well as immunohistochemistry (IHC)-based methodologies, for the same clinical indication, will not be covered."

Circulating Tumor Cell (CTC) Enumeration Analysis
National Comprehensive Cancer Network (NCCN)
NCCN Breast Cancer guidelines (4.2024) mention that guidance for clinical use of circulating tumor cells (CTC) in metastatic breast cancer assessment and monitoring is not currently part of the guideline. Studies mentioned showed that enumeration of circulating tumor cells did not have predictive value. (p. MS-75)

Centers for Medicare and Medicaid Services
In the CMS local coverage determination (LCD) "MolDX: Phenotype Biomarker Detection in Circulating Tumor Cells," the following is included regarding CTC enumeration analysis: "CTC enumeration may be a good prognostic indicator for certain cancers, but studies do not conclusively suggest a clear effect on outcomes resulting from a change in management."

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14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary [CUP]). Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
17. 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
	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
	0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden ***(Code effective 10/1/2024)***
	0487U	Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidy-corrected gene copy number amplifications and

Type	Code	Description
		losses, gene rearrangements, and microsatellite instability ***(Code effective 10/1/2024)***
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular-weight melanoma-associated antigen, CD34 and CD45 protein biomarkers, peripheral blood
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker-expressing cells, peripheral blood ***(Code effective 10/1/2024)***
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker-expressing cells, peripheral blood ***(Code effective 10/1/2024)***
	0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffin-embedded (FFPE) tissue, next-generation sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection ***(Code effective 10/1/2024)***
	0530U	Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy-number alterations, with therapy association ***(Code effective 1/1/2025)***
	0539U	Oncology (solid tumor), cell-free circulating tumor DNA (ctDNA), 152 genes, next-generation sequencing, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant ***(Code effective 4/1/2025)***
	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 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,

Type	Code	Description
		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
	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
	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);
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.
02/01/2025	Annual review. Policy statement, guidelines and literature updated. Coding update.
05/01/2025	Coding update.

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 (No changes)	
BEFORE	**AFTER**
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, **OR** 2. Stage IV or metastatic large cell lung carcinoma, **OR** 3. Stage IV or metastatic squamous cell lung carcinoma, **OR** 4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR** 5. Locally advanced or metastatic pancreatic adenocarcinoma, **OR** 6. Metastatic or advanced gastric cancer, **OR** 7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR** 8. Metastatic prostate cancer, **OR** 9. Stage III or higher cutaneous melanoma**, OR** 10. Metastatic colorectal cancer, **OR** 11. Locally advanced or metastatic ampullary adenocarcinoma, **OR** 12. Persistent or recurrent cervical cancer**, OR** 13. Unresectable or metastatic biliary tract cancer**, OR** 14. Suspected or confirmed histiocytic neoplasm, **OR** 15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR** 16. Locoregional unresectable or metastatic large or small cell carcinoma, **OR**	**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, **OR** 2. Stage IV or metastatic large cell lung carcinoma, **OR** 3. Stage IV or metastatic squamous cell lung carcinoma, **OR** 4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR** 5. Locally advanced or metastatic pancreatic adenocarcinoma, **OR** 6. Metastatic or advanced gastric cancer, **OR** 7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR** 8. Metastatic prostate cancer, **OR** 9. Stage III or higher cutaneous melanoma**, OR** 10. Metastatic colorectal cancer, **OR** 11. Locally advanced or metastatic ampullary adenocarcinoma, **OR** 12. Persistent or recurrent cervical cancer**, OR** 13. Unresectable or metastatic biliary tract cancer**, OR** 14. Suspected or confirmed histiocytic neoplasm, **OR** 15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR** 16. Locoregional unresectable or metastatic large or small cell carcinoma, **OR**

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
17. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm**, OR** 18. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR** 19. Recurrent ovarian, fallopian tube or primary peritoneal cancer**, OR** 20. Recurrent or stage IV breast cancer, **AND** B. If a broad molecular profiling panel test via circulating tumor DNA is being performed simultaneously with solid tumor tissue testing, the member must have one of the following diagnoses: 1. Lung adenocarcinoma, **OR** 2. Large cell lung carcinoma, **OR** 3. Squamous cell lung carcinoma, **OR** 4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS). II. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455, 81462, 81463, 81464) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.	17. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm**, OR** 18. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR** 19. Recurrent ovarian, fallopian tube or primary peritoneal cancer**, OR** 20. Recurrent or stage IV breast cancer, **AND** B. If a broad molecular profiling panel test via circulating tumor DNA is being performed simultaneously with solid tumor tissue testing, the member must have one of the following diagnoses: 1. Lung adenocarcinoma, **OR** 2. Large cell lung carcinoma, **OR** 3. Squamous cell lung carcinoma, **OR** 4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS). II. Broad molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445, 81455, 81462, 81463, 81464) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA) III. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 0388U, 81210, 81235, 81275, 81462, 81479) may be considered **medically necessary** when: A. The member has a diagnosis or progression of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma, **OR** 2. Advanced or metastatic large cell lung carcinoma, **OR** 3. Advanced or metastatic squamous cell lung carcinoma, **OR** 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).	**Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)** III. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 0388U, 81210, 81235, 81275, 81462, 81479) may be considered **medically necessary** when: A. The member has a diagnosis or progression of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma, **OR** 2. Advanced or metastatic large cell lung carcinoma, **OR** 3. Advanced or metastatic squamous cell lung carcinoma, **OR** 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
IV. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 0388U, 81210, 81235, 81275, 81462, 81479) are considered **investigational** for all other indications.	IV. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 0388U, 81210, 81235, 81275, 81462, 81479) are considered **investigational** for all other indications.
Single Gene Molecular Profiling Panel Tests Via Circulating Tumor DNA (ctDNA) ***EGFR* Variant Analysis via ctDNA** V. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA) is considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma, **OR** 2. Advanced or metastatic large cell lung carcinoma, **OR** 3. Advanced or metastatic squamous cell lung carcinoma, **OR** 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND** B. Treatment with an *EGFR* tyrosine kinase inhibitor therapy (examples: erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) is being considered.	**Single Gene Molecular Profiling Panel Tests Via Circulating Tumor DNA (ctDNA)** ***EGFR* Variant Analysis via ctDNA** V. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA) is considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of **any** of the following: 1. Advanced or metastatic lung adenocarcinoma, **OR** 2. Advanced or metastatic large cell lung carcinoma, **OR** 3. Advanced or metastatic squamous cell lung carcinoma, **OR** 4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND** B. Treatment with an *EGFR* tyrosine kinase inhibitor therapy (examples: erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) is being considered.
VI. *EGFR* variant analysis (81235) via circulating tumor DNA (ctDNA), as a stand alone test, is considered **investigational** for all other indications.	VI. *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** VII. *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, **OR** 2. The member has stage III or higher cutaneous melanoma, **AND** a. Is being considered for adjuvant or other systemic therapy, **OR**	***BRAF* Variant Analysis via ctDNA** VII. *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, **OR** 2. The member has stage III or higher cutaneous melanoma, **AND** a. Is being considered for adjuvant or other systemic therapy, **OR**

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** a. Is being considered for anticancer therapy.	3. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** a. Is being considered for anticancer therapy.
VIII. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.	VIII. *BRAF* variant analysis (81210) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.
***KRAS* Variant Analysis via ctDNA**	***KRAS* Variant Analysis via ctDNA**
IX. *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, **OR** B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** 1. Is being considered for anticancer therapy.	IX. *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, **OR** B. The member has locally advanced or metastatic pancreatic adenocarcinoma, **AND** 1. Is being considered for anticancer therapy.
X. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.	X. *KRAS* variant analysis (81275, 81276) via circulating tumor DNA (ctDNA) is considered **investigational** for all other indications.
***PIK3CA* Variant Analysis via ctDNA**	***PIK3CA* Variant Analysis via ctDNA**
XI. *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, **AND** B. The member is considering treatment with alpelisib plus fulvestrant, or capivasertib plus fulvestrant, **AND** C. The member has had progression on at least one line of therapy.	XI. *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, **AND** B. The member is considering treatment with alpelisib plus fulvestrant, or capivasertib plus fulvestrant, **AND** C. The member has had progression on at least one line of therapy.
XII. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA), is considered **investigational** for all other indications.	XII. *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**	**Circulating Tumor Cell Tests** **AR-V7 Circulating Tumor Cells (CTC) Analysis**

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
XIII. 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, **AND** B. Tissue-based testing is not feasible for the member, **AND** C. The test is ordered only once during the current cancer diagnosis, **AND** D. The member has at least **one** of the following: 1. Newly metastatic cancer, **OR** 2. Signs of clinical, radiological or pathologic disease progression.	XIII. 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, **AND** B. Tissue-based testing is not feasible for the member, **AND** C. The test is ordered only once during the current cancer diagnosis, **AND** D. The member has at least **one** of the following: 1. Newly metastatic cancer, **OR** 2. Signs of clinical, radiological or pathologic disease progression.
XIV. AR-V7 circulating tumor cells (CTC) analysis (81479) is considered **investigational** for all other indications.	XIV. AR-V7 circulating tumor cells (CTC) analysis (81479) is considered **investigational** for all other indications.
Circulating Tumor Cell (CTC) Enumeration XV. Circulating Tumor Cell (CTC) enumeration (86152) is considered **investigational**.	**Circulating Tumor Cell (CTC) Enumeration** XV. Circulating Tumor Cell (CTC) enumeration (86152) is considered **investigational**.