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

OVERVIEW

Cell-free circulating tumor DNA (ctDNA or cfDNA) originates directly from the tumor tissue (primary or metastasis). As tumor cells die the contents are released into the bloodstream. Genetic tests performed on circulating tumor DNA (ctDNA), also referred to as a liquid biopsy, potentially offer a noninvasive alternative to tissue biopsy for detection of "driver mutations" or acquired genetic mutations that may guide targeted therapy, and may also be used to track progression of disease.

Circulating tumor cells (CTCs) are intact tumor cells that are shed from tumor cells into the bloodstream or lymphatic system. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic rather than for guiding therapeutic choices, through quantification of circulating levels.

POLICY REFERENCE 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.

Coverage Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)				
Broad Molecular Profiling Panel Tests via Circulating	FoundationOne Liquid CDx (Foundation Medicine)	0239U	C15, C16, C18, C25, C34, C61	1, 2, 3, 4, 5, 6, 7, 8,
	Guardant360 CDx (Guardant Health)	0242U		

Tumor DNA (ctDNA)	Guardant360 83+ genes (Guardant Health)	0326U		11, 12, 13, 14, 15, 16, 17
	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	C34	1
	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	C34	1, 9, 10
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600, Blood (Mayo Medical Laboratories)	81210	C18-C21, C43	1, 3, 4, 8
	BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR (ARUP Laboratories)			
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81275, 81276	C18-C20	1, 3, 8
PIK3CA Variant Analysis via ctDNA	therascreen PIK3CA RGQ PCR Kit (QIAGEN)	0177U	C50	5
	PIK3CA Mutation CDx - Plasma (NeoGenomics Laboratories)	81309		
Circulating Tumor Cell (CTC) Tests				
AR-V7 Androgen	AR-V7 Nucleus Detect (Epic Sciences)	81479	C61, Z19.2	2

Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)				
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH HER2 Circulating Tumor Cell Test (Menarini Silicon Biosystems)	0338U	C00.0-C96.9	5
	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		

OTHER RELATED POLICIES

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

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.
- ***Oncology*: *Algorithmic Testing*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to circulating tumor DNA or circulating tumor cell testing that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

MOLECULAR PROFILING PANEL TESTS VIA CIRCULATING TUMOR DNA (ctDNA)

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

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

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

      1. Stage IV or metastatic lung adenocarcinoma, **OR**
      2. Stage IV or metastatic large cell lung carcinoma, **OR**
      3. Stage IV or metastatic squamous cell lung carcinoma, **OR**
      4. Stage IV or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
      5. Locally advanced/metastatic pancreatic adenocarcinoma, **OR**
      6. Metastatic or advanced gastric cancer, **OR**
      7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**
      8. Metastatic prostate cancer, **OR**
      9. Stage III or higher cutaneous melanoma**, OR**
      10. Metastatic colorectal cancer, **OR**
      11. Locally advanced or metastatic ampullary adenocarcinoma, **OR**

12. Persistent or recurrent cervical cancer**, OR**
13. Unresectable or metastatic biliary tract cancer**, OR**
14. Suspected or confirmed histiocytic neoplasm, **OR**
15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma or large or small cell carcinoma or mixed neuroendocrine-non-neuroendocrine neoplasm**, OR**
16. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**
17. Recurrent ovarian, fallopian tube or primary peritoneal cancer**, OR**
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**.

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

I. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) (0179U, 81210, 81235, 81275, 81462, 81479, 0388U) are considered **medically necessary** when:

A. The member has a diagnosis or progression of any 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).

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

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

EGFR Variant Analysis via ctDNA

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

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

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

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

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

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BRAF Variant Analysis via ctDNA

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

A. The member meets one of the following:

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

a) Testing for *NRAS* and *KRAS* is also being performed, either as separate tests or as part of a panel, **OR**

2. The member has stage III or higher cutaneous melanoma, **AND**

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

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

a) Is being considered for anticancer therapy.

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

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KRAS Variant Analysis via ctDNA

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

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

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

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

1. Is being considered for anticancer therapy.

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

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PIK3CA Variant Analysis via ctDNA

I. *PIK3CA* variant analysis (0177U, 81309) via circulating tumor DNA (ctDNA) is considered **medically necessary** when:

   A. The member has recurrent, unresectable, or stage IV hormone receptor-positive/HER2-negative breast cancer, **AND**

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

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

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

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CIRCULATING TUMOR CELL TESTS

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

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

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

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

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

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Circulating Tumor Cell (CTC) Enumeration

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

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DEFINITIONS

1. **Circulating tumor DNA (ctDNA):** Fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.
2. **Circulating Tumor Cells (CTCs):** Intact cells that have shed into the bloodstream or lymphatic system from a primary tumor or a metastasis site, and are carried around the body by blood circulation.

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CLINICAL CONSIDERATIONS

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

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

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

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BACKGROUND AND RATIONALE

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).

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