Medica Central Coverage Policy

Policy Name:	**Genetic Testing – Oncology Testing: Solid Tumor Molecular Diagnostics MP9608**
Effective Date:	**July 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

This policy addresses the use of molecular profiling for a known or suspected solid tumor (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), cytogenetic / fusion testing, or circulating tumor DNA (ctDNA)).

While the primary goal of this testing is to identify biomarkers that diagnose cancer, or give prognostic and treatment selection information, this testing also has the potential to uncover clinically relevant germline variations that are associated with a hereditary cancer susceptibility syndrome, and other conditions, if confirmed to be present in the germline. Providers should communicate the potential for these incidental findings with their patients prior to somatic mutation profiling.

For additional information see the Rationale section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Molecular Profiling Panels			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels	FoundationOne CDx - 0037U (Foundation Medicine)	81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U , 0391U, 0473U, 0523U, C00-D49, Z85	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 29
	MSK-IMPACT - 0048U (Memorial Sloan Kettering Medical Center)		
	Oncomap ExTra - 0329U (Exact Sciences)		
	OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs)		
	Precise Tumor (Myriad) Tempus xT CDx - 0473U (Tempus) Guardant360 TissueNext - 0334U (Guardant)		
	PGDx elio tissue complete - 0250U (Personal Genome Diagnostics, Inc		
	OmniSeq INSIGHT (Labcorp)		
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)		
	Solid Tumor Expanded Panel - 0379U (Quest Diagnostics)		
	UW OncoPlex Cancer Gene Panel (University of Washington)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Strata Select - 0391U (Strata Oncology)		
	oncoRevealTM CDx - 0523U (Pillar Biosciences, Inc)		
Targeted RNA Fusion Panels for Solid Tumors	Targeted Solid Tumor NGS Fusion Panel (NeoGenomics)	81449, C91, C34, C71, C49, C96	1, 6, 7, 11, 16, 17
Broad RNA Fusion Panels for Solid Tumor	Aventa FusionPlus - 0444U (Aventa Genomics)	81455, 81456, 0444U, C00-C80	
	OnkoSight Advanced Comprehensive Gene Fusion NGS Panel (BioReference Laboratories) Cancer Gene-Fusion Panel (Children's Hospital of Philadelphia - Division of Genomic Diagnostics)		
Colorectal Cancer Focused Molecular Profiling Panels	Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)	81445, 81457, C18-C20	2
	COLONSEQPlus Panel (MedFusion)		
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test - 0022U (Thermo Fisher Scientific) OnkoSight Advanced Lung Cancer NGS Panel (BioReference Laboratories)	81457, 0022U, 0478U, C34	1

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Lung HDPCR - 0478U (Protean BioDiagnostics)		
Cutaneous Melanoma Focused Molecular Profiling Panels	MelanomaSeqPlus (Quest Diagnostics)	81445, 81457, C43, D03	18
	OnkoSight Advanced Melanoma NGS Panel (BioReference Laboratories)		
Single Gene Testing of Solid Tumors			
Tumor Specific *BRAF* Variant Analysis	BRAF Mutation Analysis (NeoGenomics)	81210, C18-C21, C34, C43, C71, C73, C91.4	1, 2, 5, 7, 9, 11, 18, 20, 21, 22, 23
Tumor Specific *BRCA1/2* Variant Analysis	BRCA1/2 Mutation Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81162, 81163, 81164, 81165, 81166, 81167, 81216, C56, C61	4, 5, 8, 24
	BRCA1/2 Mutation Analysis for Tumors (NeoGenomics Laboratories)		
Tumor Specific *EGFR* Variant Analysis	EGFR Mutation Analysis by PCR (NeoGenomics Laboratories)	81235, C34	1
Tumor Specific *ESR1* Variant Analysis	ESR1 Mutations Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81479, C50	3
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (Labcorp)	88360, C56	4
Tumor Specific *IDH1* and *IDH2* Variant Analysis (Solid Tumor)	IDH1/IDH2 Mutation Analysis by PCR (NeoGenomics)	81120, 81121, 0481U, C71, C92, D49.6	7

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	IDH1, IDH2, and TERT Mutation Analysis, Next Generation Sequencing, Tumor (IDTRT) - 0481U (Mayo Clinic)		
Tumor Specific *KIT* Variant Analysis	KIT Mutation Analysis (ProPath) KIT (D816V) Digital PCR in Systemic Mastocytosis (Labcorp)	81272, 81273, C43, C49.A, C92, D47.1, D47.02	18, 19, 26
Tumor Specific *KRAS* Variant Analysis	KRAS Mutation Analysis by PCR (NeoGenomics)	81275, 81276, C18-21, C34	1, 2, 5, 27
Tumor Specific *MGMT* Methylation Analysis	MGMT Promoter Methylation - Tumor (Ohio State University Molecular Pathology Laboratory)	81287, C71	7
Tumor Specific *MLH1* Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics)	81288, C18-C21, C54.1	2, 28
Tumor Specific Microsatellite Instability (MSI) Analysis	Microsatellite Instability (MSI) by PCR (NeoGenomics Laboratories) Microsatellite Instability (MSI) (Quest Diagnostics)	81301, C15-C23, C50, C53, C54.1, C62, C80	3, 4, 5, 8, 9, 10, 12, 20, 22, 23, 27, 29, 30, 31, 32, 33, 34, 36
Tumor Specific *NRAS* Variant Analysis	NRAS Mutation Analysis (NeoGenomics)	81311, C18-C21	2
Tumor Specific PD-L1 Protein Analysis	PD-L1, IHC with Interpretation (Quest Diagnostics)	88341, 88342, 88360, 88361, C11, C15, C16, C34, C50, C51, C53, C67	1, 3, 9, 22, 31, 33, 35, 40, 43, 44, 45
Tumor Specific *PIK3CA* Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309, 0155U, C50, C55	3, 33

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	PIK3CA Mutation Analysis, therascreen - QIAGEN - 0155U (LabCorp)		
Tumor Mutational Burden (TMB) Testing			
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479, C00-D49, Z85	3, 4, 5, 8, 9, 10, 12, 20, 22, 23, 27, 29, 30, 31, 32, 33, 34, 35, 36
Measurable (Minimal) Residual Disease (MRD) Testing			
Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing	Signatera - Residual Disease Test (MRD) - 0340U (Natera) Guardant Reveal (Guardant Health) Guardant360 Response - 0422U (Guardant Health)	81479, 0340U, 0422U, C00-D49, Z85	46, 47
Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing	Colvera - 0229U (Clinical Genomics Pathology, Inc.)	0229U, 0306U, 0307U, 0486U, 0498U, 0501U, C00-D49, Z85	
	Invitae PCM Tissue Profiling and MRD Baseline Assay - 0306U (Invitae)		
	Invitae PCM MRD Monitoring - 0307U (Invitae)		
	Northstar Response - 0486U (BillionToOne)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	OptiSeq Colorectal Cancer NGS Panel - 0498U (DiaCarta Inc.)		
	QuantiDNA Colorectal Cancer Triage Test - 0501U (DiaCarta Inc.)		
HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing	NavDx - 0356U (Naveris)	0356U, C10.9	46, 47
Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)			
Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)	FoundationOne Liquid CDx - 0239U (Foundation Medicine)	81445, 81455, 81462, 81463, 81464, 0239U, 0242U, 0326U, 0409U, 0485U, 0487U, 0499U, 0530U, C15, C16, C18, C25, C34, C61	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 18, 22, 27, 34, 40
	Guardant360 - 0326U (Guardant Health) Guardant360 CDx - 0242U (Guardant Health) Guardant360 83+ genes (Guardant Health)		
	NeoLAB Solid Tumor Liquid Biopsy (NeoGenomics Laboratories) Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus) LiquidHALLMARK - 0409U (Lucence Health) Caris Assure - 0485U (Caris Life Sciences)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Northstar Select - 0487U (BillionToOne)		
	OptiSeq Dual Cancer Panel Kit - 0499U (DiaCarta, Inc)		
	LiquidHALLMARK - 0530U (Lucence Health, Inc)		
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung - 0179U (Labcorp) OncoBEAM Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc.) InVisionFirst-Lung Liquid Biopsy - 0388U (NeoGenomics) GeneStrat NGS (Biodesix)	81210, 81235, 81275, 81462, 81479, 0179U, 0388U, C34	1
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)			
EGFR Variant Analysis via ctDNA	EGFR ultrasensitive "liquid biopsy" (Brigham and Women's Hospital - Center for Advanced Molecular Diagnostics)	81235, C34	1, 48
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600, Blood (Mayo Medical Laboratories) BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR (ARUP Laboratories)	81210, C18-C21, C43	2, 5, 18

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81275, 81276, C18-C20	2, 5
PIK3CA Variant Analysis via ctDNA	therascreen PIK3CA RGQ PCR Kit - 0177U (QIAGEN)	81309, 0177U, C50	3
	Cell-Free DNA PIK3CA Test, Blood (Mayo Medical Laboratories)		
Circulating Tumor Cell (CTC) Tests			
AR-V7 Circulating Tumor Cells (CTC) Analysis	AR-V7 (Epic Sciences)	81479, C61	49
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test - 0337U (Menarini Silicon)	0337U, 0338U, 0490U, 0491U, 0492U, C00.0-C96.9	3, 49
	CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test - 0338U (Menarini Silicon)		
	CELLSEARCH Circulating Melanoma Cell (CMC) Test - 0490U (Menarini Silicon)		
	CELLSEARCH ER Circulating Tumor Cell (CTC-ER) Test - 0491U (Menarini Silicon)		
	CELLSEARCH PD-L1 Circulating Tumor Cell (CTC-PDL1) Test - 0492U (Menarini Silicon)		
Cytogenetic Tumor Testing			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests	ALK FISH, Non-Small cell Lung Cancer (Labcorp)	88271, 88274, C34, C73	1, 5, 11, 12, 20, 37
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion Bladder Kit (Quest Diagnostics)	88120, 88121, C67, R31.9, Z85, Z85.5	38, 39
Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (IHC, FISH, and CISH)	ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue (ARUP Laboratories)	88360, 88377, C08, C15, C16, C18, C19, C20, C50	2, 3, 4, 5, 9, 22, 23, 29, 33, 35, 40, 43
NTRK Fusion Analysis Panel	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194, C15, C16, C18, C34, C49.9, C50, C51, C53, C54, C73, C80.1, C91	1, 2, 3, 4, 5, 6, 9, 10, 14, 16, 20, 22, 23, 25, 29, 31, 33, 34, 35, 37, 40, 41, 42
Tumor Specific *RET* Gene Rearrangement Tests (FISH)	RET FISH (NeoGenomics Laboratories) Oncology FISH Analysis - RET Rearrangement (Baylor Genetics, LLC)	88271, 88275, 88291, 88374, 88377, C34, C53, C73	1, 2, 3, 5, 9, 20, 22, 35, 40
Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274, 88342, 88366, C34	1, 5, 37
Cancer Exome and Genome Sequencing			
Cancer Exome and Genome Sequencing	Somatic Whole Genome Sequencing - 0297U (Praxis Genomics)	81415, 81416, 81425, 81426, 0297U, 0036U, C00-D49, Z85	15

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine) Tempus xE (Tempus AI, Inc)		

RELATED POLICIES

This policy document provides coverage criteria for testing related to molecular analysis of solid tumors. Please refer to:

- ***Oncology Testing: Hematologic Malignancy Molecular Diagnostics*** for coverage criteria related to molecular profiling of a known or suspected blood cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Oncology Testing: Hereditary Cancer*** for coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology Testing: Cancer Screening and Surveillance*** for coverage criteria related to screening and biomarker cancer tests.
- ***Oncology Testing: Algorithmic Assays*** for coverage criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***General Approach to Laboratory Testing*** for coverage criteria related to molecular testing for solid tumors, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

back to top

COVERAGE CRITERIA

MOLECULAR PROFILING PANELS

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

I. Tumor-type agnostic solid tumor molecular profiling panels are considered **medically necessary** when:

A. The member meets both of the following:

1. The member has a diagnosis of:

a) Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**

b) Histiocytosis**, OR**

c) Non-small cell lung cancer (NSCLC) regardless of stage, **OR**

d) Resectable or borderline resectable pancreatic adenocarcinoma, **OR**

e) Central nervous system tumor, **AND**

2. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**

B. The member meets one of the following:

1. The member is being evaluated for a suspected metastatic malignancy of unknown type, **OR**

2. The member is undergoing initial evaluation for a known or suspected gastric cancer, **OR**

3. The member has a diagnosis of uterine neoplasm, **AND**

a) The member is undergoing initial evaluation, **OR**

4. The member undergoing initial evaluation for a known or suspected gastrointestinal stromal tumor (GIST), **AND**

a) The tumor is negative for *KIT* and *PDGFRA* mutations.

II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel is considered **medically necessary** when:

A. The member has progression of:

1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**

2. Advanced or metastatic gastric adenocarcinoma, **OR**

3. Metastatic prostate cancer.

III. Tumor-type agnostic solid tumor molecular profiling panels are considered **investigational** for all other indications.

NOTE: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes.

view rationale

back to top

Targeted RNA Fusion Panels for Solid Tumors

I. Targeted RNA fusion panels for solid tumors with 5-50 genes performed on peripheral blood, bone marrow or solid tumors are considered **medically necessary** when:

A. The member has a diagnosis of, or is undergoing workup for:

1. Glioma, **OR**

2. Histiocytosis, **OR**

3. Sarcoma, **OR**

B. The member has a gastrointestinal stromal tumor, **AND**

1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations, **OR**

C. The member has non-small cell lung cancer, **AND**

1. DNA-based NGS tumor profiling was negative for actionable mutations, **OR**

D. The member has a metastatic or advanced solid tumor, **AND**

1. There is a fusion-targeted therapy with regulatory approval for that cancer type, **OR**

2. DNA-based panel testing was negative for oncogenic driver mutations.

II. Targeted RNA fusion panels for solid tumors with 5-50 genes performed on peripheral blood, bone marrow or solid tumors are considered **investigational** for all other indications.

view rationale

back to top

Broad RNA Fusion Panels for Solid Tumors

I. Broad RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone that are performed on solid tumors are considered **investigational** for all indications.

view rationale

back to top

Colorectal Cancer Focused Molecular Profiling Panels

I. Colorectal cancer focused molecular profiling panels in solid tumors are considered **medically necessary** when:

   A. The member has suspected or proven metastatic colorectal cancer, **AND**

   B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.*

II. Colorectal cancer-focused molecular profiling panels are considered **investigational** for all other indications.

NOTE: If a panel is performed, appropriate panel codes should be used.

view rationale

back to top

Lung Cancer Focused Molecular Profiling Panels

I. Lung cancer focused molecular profiling panels are considered **medically necessary** when:

   A. The member has a diagnosis of:

      1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**

      2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**

      3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**

      4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**

   B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy).

II. Repeat lung cancer-focused molecular profiling panels are considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer.

III. Lung cancer-focused molecular profiling panels are considered **investigational** for all other indications.

NOTE: If a panel is performed, appropriate panel codes should be used.

view rationale

back to top

Cutaneous Melanoma Focused Molecular Profiling Panels

I. Cutaneous melanoma focused molecular profiling panels are considered **medically necessary** when:

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

1. Stage III melanoma or higher, **OR**

2. Recurrent melanoma, **AND**

B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **AND**

C. One of the following:

1. The member has not had previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis, **OR**

2. The member **has** had previous somatic testing via a multigene cancer panel for a primary melanoma diagnosis, and has a **new** primary melanoma diagnosis for which this testing is being ordered.

II. Cutaneous melanoma focused molecular profiling panels are considered **investigational** for all other indications.

NOTE: If a panel is performed, appropriate panel codes should be used.

view rationale

back to top

SINGLE GENE TESTING OF SOLID TUMORS

Tumor Specific *BRAF* Variant Analysis

I. Tumor specific *BRAF* variant analysis in solid tumors and hematologic malignancies is considered **medically necessary** when:

A. The member has a diagnosis of:

1. Suspected or proven metastatic colorectal cancer, **OR**

2. Advanced or metastatic non-small-cell lung cancer (NSCLC), **OR**

3. Stage III or stage IV cutaneous melanoma, **OR**

4. Indeterminate thyroid nodules requiring biopsy, **OR**

5. Anaplastic thyroid carcinoma, **OR**

6. Locally recurrent, advanced and/or metastatic papillary thyroid cancer, **OR**

7. Locally recurrent, advanced and/or metastatic follicular thyroid cancer, **OR**

8. Locally recurrent, advanced and/or metastatic Hurthle cell thyroid carcinoma, **OR**

9. Low-grade glioma or pilocytic astrocytoma, **OR**

10. Resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma, **OR**

11. Metastatic small bowel adenocarcinoma, **OR**

12. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**

13. Locally advanced, recurrent or metastatic gastric cancer, **OR**

B. The member is being evaluated for:

1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype), **OR**

2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).

view rationale

back to top

Tumor Specific *BRCA1/2* Variant Analysis

I. Tumor specific *BRCA1/2* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of:

1. Ovarian, fallopian tube and/or primary peritoneal cancer, **OR**

2. Metastatic prostate cancer, **OR**

3. Pancreatic cancer.

view rationale

back to top

Tumor Specific *EGFR* Variant Analysis

I. Tumor specific *EGFR* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of:

1. Stage IB or higher lung adenocarcinoma, **OR**

2. Stage IB or higher large cell lung carcinoma, **OR**

3. Stage IB or higher squamous cell lung carcinoma, **OR**

4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

view rationale

back to top

Tumor Specific *ESR1* Variant Analysis

I. Tumor specific *ESR1* variant analysis in solid tumors is considered **medically necessary** when:

A. The member is one of the following:

1. Premenopausal female (sex assigned at birth) receiving ovarian ablation or suppression, **OR**

2. Postmenopausal female (sex assigned at birth), **OR**

3. Adult male (sex assigned at birth), **AND**

B. The member has a diagnosis of ER-positive and *HER2*-negative breast cancer, **AND**

C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a *CDK4/6* inhibitor.

view rationale

back to top

Tumor Specific *FOLR1* Protein Analysis

I. Tumor specific *FOLR1* protein expression analysis via immunohistochemistry (IHC) analysis is considered **medically necessary** when:

A. The member has recurrent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.

view rationale

back to top

Tumor Specific *IDH1* and *IDH2* Variant Analysis (Solid Tumor)

I. Tumor specific *IDH1* and *IDH2* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of glioma.

view rationale

back to top

Tumor Specific *KIT* Variant Analysis

I. Tumor specific *KIT* variant analysis in solid tumors or hematologic malignancies is considered **medically necessary** when:

A. The member is being evaluated for systemic mastocytosis, **OR**

B. The member has a diagnosis of acute myeloid leukemia (AML), **OR**

C. The member has stage IV cutaneous melanoma, **OR**

D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST).

view rationale

back to top

Tumor Specific *KRAS* Variant Analysis

I. Tumor specific *KRAS* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has suspected or proven metastatic colorectal cancer, **OR**

B. The member has advanced or metastatic non-small cell lung cancer, **OR**

C. The member has pancreatic adenocarcinoma, **OR**

D. The member has unresectable or metastatic gallbladder cancer, **OR**

E. The member has unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma.

view rationale

back to top

Tumor Specific *MGMT* Methylation Analysis

I. Tumor specific *MGMT* promoter methylation analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of high grade (grade 3 or 4) glioma.

view rationale

back to top

Tumor Specific *MLH1* Methylation Analysis

I. Tumor specific *MLH1* promoter methylation analysis in solid tumors is considered **medically necessary** when:

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

1. Colorectal cancer, **OR**

2. Endometrial (uterine) cancer, **AND**

B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis.

view rationale

back to top

Tumor Specific Microsatellite Instability (MSI) Analysis

I. Tumor specific microsatellite instability (MSI) analysis in solid tumors is considered **medically necessary** when:

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

1. Colorectal cancer, **OR**
2. Endometrial cancer, **OR**
3. Gastric cancer, **OR**
4. Esophageal and esophagogastric junction cancer, **OR**
5. Recurrent, progressive or metastatic cervical carcinoma, **OR**
6. Testicular cancer with progression after high dose chemotherapy or third-line therapy, **OR**
7. Unresectable or metastatic gallbladder cancer, **OR**
8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma, **OR**
9. Recurrent unresectable or metastatic breast cancer, **OR**
10. Small bowel adenocarcinoma, **OR**
11. Resectable, borderline resectable, or metastatic pancreatic cancer, **OR**
12. Metastatic occult primary, **OR**
13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva**, OR**
14. Metastatic chondrosarcoma, **OR**
15. Metastatic chordoma, **OR**
16. Widely metastatic Ewing sarcoma, **OR**
17. Metastatic osteosarcoma, **OR**
18. Recurrent or metastatic vaginal cancer, **OR**
19. Recurrent ovarian cancer.

view rationale

back to top

Tumor Specific *NRAS* Variant Analysis

I. Tumor specific *NRAS* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has suspected or proven metastatic colorectal cancer.

view rationale

back to top

Tumor Specific PD-L1 Protein Analysis

I. PD-L1 protein expression analysis via immunohistochemistry (IHC) in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of or is in the initial work up stage for:

1. Stage IB or higher lung adenocarcinoma, **OR**
2. Stage IB or higher large cell lung carcinoma, **OR**
3. Stage IB or higher squamous cell lung carcinoma, **OR**
4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Locally advanced or metastatic bladder cancer, **OR**
6. Recurrent, progressive, or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), **OR**
7. Recurrent unresectable or stage IV triple negative breast cancer, **OR**
8. Locally advanced, recurrent or metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**
9. Locally advanced, recurrent or metastatic gastric adenocarcinoma, **OR**
10. Recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal cancer, **OR**
11. Recurrent, progressive or metastatic squamous cell vulvar cancer, **OR**
12. Recurrent or metastatic vaginal cancer.

NOTE: PD-L1 protein expression analysis via IHC is often performed as an adjunct component of comprehensive molecular profiling panels for solid tumors

view rationale

back to top

Tumor Specific *PIK3CA* Variant Analysis

I. Tumor specific *PIK3CA* variant analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of recurrent unresectable or stage IV, HR positive, HER2-negative invasive breast cancer, **OR**

B. The member has a distantly metastatic salivary gland tumor.

view rationale

back to top

TUMOR MUTATIONAL BURDEN (TMB) TESTING

Tumor Mutational Burden (TMB)

I. Tumor mutational burden (TMB) testing is considered **medically necessary** when:

A. The member has a diagnosis of:

1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **AND**

B. The member has had progression of the cancer following prior treatment, **AND**

C. The member has no remaining satisfactory treatment options, **AND**

D. The member does not have central nervous system cancer.

view rationale

back to top

MEASURABLE (MINIMAL) RESIDUAL DISEASE (MRD) TESTING

Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing

I. Minimal residual disease (MRD) analysis for solid tumors using cell-free DNA with sufficient evidence of clinical utility and validity is considered **medically necessary** when**:**

A. The identification of recurrent, refractory, or progressive disease will require a change in management, **AND**

B. The member is not undergoing concurrent molecular laboratory testing for surveillance or monitoring for recurrent, refractory, or progressive disease, **AND**

C. The member meets one of the following:

1. The member is currently being treated for cancer, **AND**

a) The test has not previously been done for this cancer diagnosis, **OR**

b) There is a clinical suspicion that the molecular profile of the member's tumor has changed, **OR**

2. The member is not currently being treated for their cancer, **AND**

    a) The test has not been done in the past 12 months, **OR**

    b) There is a clinical suspicion for tumor recurrence, **AND**

D. The member meets one of the following:

1. The member is being tested via Guardant360 Response or Guardant Reveal and has one of the following:

    a) Metastatic colon cancer, **OR**

    b) Colon cancer at any stage, **AND**

        (1) The member is being monitored for response to immune checkpoint inhibitor therapy, **OR**

2. The member is being tested via Signatera and has one of the following:

    a) Metastatic colon cancer, **OR**

    b) Muscle invasive bladder cancer, **OR**

    c) Ovarian cancer, **OR**

    d) Neoadjuvant (pre-surgery) breast cancer, **OR**

    e) Any solid tumor, **AND**

        (1) The member is being monitored for response to immune checkpoint inhibitor therapy.

II. Minimal residual disease (MRD) analysis with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated.

view rationale

back to top

Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing

I. Minimal residual disease (MRD) analysis with insufficient evidence of clinical validity using solid tumor tissue is considered **investigational**.

view rationale

back to top

HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing

I. Minimal residual disease (MRD) analysis for HPV-related head and neck cancers using cell-free DNA is **medically necessary** when:

A. The member has a personal history of HPV-driven oropharyngeal cancer, **AND**

B. The identification of recurrence or progression of disease will require a change in management, **AND**

C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, **AND**

D. The member meets one of the following:

1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND**

a) The test has not previously been done for this episode of cancer, **OR**

2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND**

a) The test has not been done in the past 12 months.

II. Minimal residual disease (MRD) analysis for HPV-related head and neck cancers using cell-free DNA is considered **investigational** for all other indications.

view rationale

back to top

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 (ctDNA) (liquid biopsy) are considered **medically necessary** when:

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

1. Metastatic lung adenocarcinoma, **OR**

2. Metastatic large cell lung carcinoma, **OR**

3. Metastatic squamous cell lung carcinoma, **OR**

4. Metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

5. Locally advanced/metastatic pancreatic adenocarcinoma, **OR**

6. Metastatic or advanced gastric cancer, **OR**

7. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**

8. Metastatic prostate cancer, **OR**

9. Stage III or higher cutaneous melanoma**, OR**

10. Metastatic colorectal cancer, **OR**

11. Locally advanced or metastatic ampullary adenocarcinoma, **OR**

12. Persistent or recurrent cervical cancer**, OR**
13. Unresectable or metastatic biliary tract cancer**, OR**
14. Suspected or confirmed histiocytic neoplasm, **OR**
15. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR**
16. Locoregional unresectable or metastatic large or small cell neuroendocrine 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 (ctDNA) 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 (ctDNA) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.

view rationale

back to top

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

I. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) are considered **medically necessary** when:

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

1. Advanced or metastatic lung adenocarcinoma, **OR**
2. Advanced or metastatic large cell lung carcinoma, **OR**
3. Advanced or metastatic squamous cell lung carcinoma, **OR**

4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

II. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) are considered **investigational** for all other indications.

view rationale

back to top

SINGLE GENE MOLECULAR PROFILING TESTS VIA CIRCULATING TUMOR DNA (CTDNA)

***EGFR* Variant Analysis via ctDNA**

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

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).

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

view rationale

back to top

***BRAF* Variant Analysis via ctDNA**

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

view rationale

back to top

KRAS Variant Analysis via ctDNA

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

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

   B. The member has locally advanced or metastatic pancreatic adenocarcinoma.

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

view rationale

back to top

PIK3CA Variant Analysis via ctDNA

I. *PIK3CA* variant analysis 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, or capivasertib plus fulvestrant, **AND**

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

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

view rationale

back to top

CIRCULATING TUMOR CELL (CTC) TESTS

AR-V7 Circulating Tumor Cells (CTC) Analysis

I. AR-V7 circulating tumor cells (CTC) analysis is considered **medically necessary** when:

   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. One of the following:

      1. The test is ordered only once during the current cancer diagnosis, **OR**

      2. The test is being performed on newly metastatic cancer, **OR**

3. The member has signs of clinical, radiological or pathologic disease progression.

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

view rationale

back to top

Circulating Tumor Cell (CTC) Enumeration

I. Circulating Tumor Cell (CTC) enumeration is considered **investigational** for all indications.

view rationale

back to top

CYTOGENETIC TUMOR TESTING

Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests

I. Somatic *ALK* gene rearrangement analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of or is in the initial work up stage for:

1. Stage IB or higher lung adenocarcinoma, **OR**
2. Stage IB or higher large cell lung carcinoma, **OR**
3. Stage IB or higher squamous cell lung carcinoma, **OR**
4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**
5. Anaplastic thyroid carcinoma, **OR**
6. Locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma, **OR**
7. Locally recurrent, advanced, and/or metastatic follicular thyroid cancer, **OR**
8. Locally advanced/metastatic ampullary adenocarcinoma, **OR**
9. Langerhans cell histiocytosis, **OR**
10. Erdheim-Chester disease, **OR**
11. Pancreatic adenocarcinoma, **OR**
12. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

view rationale

back to top

Bladder Cancer Diagnostic and Recurrence FISH Tests

I. Bladder cancer diagnostic and recurrence FISH tests for diagnosing and monitoring bladder cancer are considered **medically necessary** when:

A. The member has hematuria, **AND**

1. Diagnostic studies have failed to identify the etiology of the hematuria, **AND**

2. A bladder cancer diagnostic and recurrence FISH test has not been ordered more than 1 time in the past 12 months, **OR**

B. The member has been treated for bladder cancer, **AND**

1. The bladder cancer diagnostic and recurrence FISH tests are ordered with the following frequency:

a) No more than 4 bladder tumor marker studies per year for years 1-2 after diagnosis

b) No more than 3 bladder tumor marker studies during year 3 after diagnosis

c) No more than 2 bladder tumor marker studies during year 4 after diagnosis

d) No more than 1 bladder tumor marker studies annually for up to 15 years after diagnosis.

II. Bladder cancer diagnostic and recurrence FISH tests for diagnosing and monitoring bladder cancer are considered **investigational** for all other indications.

view rationale

back to top

Tumor Specific *ERBB2 (HER2)* Deletion/Duplication (IHC, FISH, and CISH)

I. Somatic *ERBB2* (*HER2*) amplification analysis via in situ hybridization (ISH) (i.e., FISH or CISH) or immunohistochemistry (IHC) in solid tumors is considered **medically necessary** when:

A. The member has any of the following:

1. Recurrent or newly diagnosed stage I-IV invasive breast cancer, **OR**

2. Inoperable locally advanced, recurrent, or metastatic gastric cancer, **OR**

3. Suspected or proven metastatic colorectal cancer or appendiceal adenocarcinoma, **OR**

4. Inoperable locally advanced, recurrent, or metastatic esophageal and/or esophagogastric junction adenocarcinoma, **OR**

5. Recurrent, unresectable, or metastatic salivary gland tumors, **OR**

6. Recurrent, advanced, or metastatic cervical carcinoma, **OR**
7. Serous endometrial carcinoma, **OR**
8. Endometrial carcinosarcoma, **OR**
9. p53 abnormal endometrial carcinoma, **OR**
10. Pancreatic adenocarcinoma, **OR**
11. Recurrent ovarian/fallopian tube/primary peritoneal cancer, **OR**
12. Recurrent or metastatic vaginal cancer, **OR**
13. Stage IIIB or higher muscle invasive bladder cancer, **OR**
14. Metastatic small bowel adenocarcinoma.

view rationale

back to top

NTRK Fusion Analysis Panel

I. *NTRK 1/2/3* fusion analysis panel via fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) in solid tumors is considered **medically necessary** when:

A. The member is undergoing initial diagnostic workup for or has a diagnosis of:

1. Advanced, progressive, or metastatic solid tumor, **OR**
2. Cancer for which surgical resection is not possible, **OR**
3. Unknown primary cancers, **OR**

B. The member has a diagnosis of any of the following cancers at any stage:

1. Cervical sarcoma, **OR**
2. Anaplastic thyroid carcinoma, **OR**
3. Acute lymphoblastic leukemia (ALL), **OR**
4. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

view rationale

back to top

Tumor Specific *RET* Gene Rearrangement Tests (FISH)

I. Tumor specific *RET* gene rearrangement testing via fluorescent in situ hybridization (FISH) in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of:

1. Recurrent, persistent locoregional, or metastatic medullary thyroid cancer, **AND**

a) Germline testing for *RET* mutations is negative or has not been done, **OR**

2. Anaplastic thyroid carcinoma, **OR**
3. Locally recurrent, advanced and/or metastatic papillary thyroid carcinoma, **OR**
4. Locally recurrent, advanced and/or metastatic follicular thyroid carcinoma, **OR**
5. Locally recurrent, advanced and/or metastatic oncocytic carcinoma (formerly called Hurthle cell carcinoma), **OR**
6. Advanced or metastatic adenocarcinoma of the lung, **OR**
7. Advanced or metastatic large cell cancer of the lung, **OR**
8. Advanced or metastatic non-small cell cancer of the lung, not otherwise specified, **OR**
9. Locally advanced or metastatic squamous cell carcinoma of the cervix, **OR**
10. Locally advanced or metastatic adenocarcinoma of the cervix, **OR**
11. Locally advanced or metastatic adenosquamous carcinoma of the cervix, **OR**
12. Recurrent unresectable or stage IV breast cancer, **OR**
13. Suspected or confirmed metastatic colon cancer, **OR**
14. Pancreatic adenocarcinoma, **OR**
15. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**
16. Locally advanced, recurrent or metastatic gastric cancer, **OR**
17. Recurrent or metastatic vaginal cancer.

view rationale

back to top

Tumor Specific *ROS1* Gene Rearrangement

I. Tumor specific *ROS1* gene rearrangement analysis in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of:

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), **OR**

5. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
6. Pancreatic adenocarcinoma, **OR**
7. Pediatric (diagnosed age 18 years or younger) diffuse high-grade glioma.

view rationale

back to top

CANCER EXOME AND GENOME SEQUENCING

Cancer Exome and Genome Sequencing

I. Cancer exome and genome sequencing in solid tumors and hematologic malignancies is considered **investigational** for all indications.

view rationale

back to top

PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

RATIONALE

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (6.2024) recommend comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer (p. BINV-18).

The NCCN guideline on Occult Primary (2.2025) recommends tumor mutation burden (TMB), MSI and MMR testing as part of the initial work up for patients with cancer of unknown primary. The guideline further recommends consideration of somatic tumor profiling to identify actionable genomic aberrations after a histological determination of the tumor has been made (p. OCC-1).

The NCCN guideline on Non-Small Cell Lung Cancer (3.2025) has several recommendations regarding biomarker testing:

- Broad molecular profiling is recommended to be performed for stage IV / advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified. NCCN also recommends consideration of broad molecular profiling for advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-14, NSCL-15, NSCL-19).
- Generally, it is recommended that broad, panel-based genomic profiling be performed via NGS when feasible. NCCN defines broad molecular profiling as a panel which includes all the following biomarkers in either one assay or several smaller assays: *EGFR, ALK, KRAS,*

ROS1, BRAF, NTRK1/2/3, *MET*ex14 skipping, *RET, ERBB2 (HER2),* and *PD-L1* (p. NSCL-19 and NSCL-H 1 and 2 of 8).

- Repeat somatic genetic testing can be helpful to aid in deciding next therapeutic steps when a patient's tumor shows evidence of progression on targeted therapy. Broad genomic profiling may be the best testing method to ensure all possible therapeutic biomarkers are analyzed (p. NSCL-H 7 of 8).

The NCCN guideline for Colon Cancer (6.2024) recommends all patients with metastatic colorectal cancer have molecular testing which should be done, if possible,via a broad NGS panel to identify rare and actionable alterations including fusions (p. COL-2, COL-B 4 of 10). Testing can be performed on the primary tumor and/or metastases (p. COL-B 4 of 10).

The NCCN guideline for Gastric Cancer (5.2024) recommends consideration of NGS testing during the workup for gastric cancer (p. GAST-1). NGS testing can be considered in place of sequential testing for individual biomarkers if there is limited tissue or traditional biopsy cannot be done in patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering an FDA approved therapy (p. GAST-B 5 of 6). The guidelines also recommend that repeat tumor testing can be considered when there is clinical or radiologic evidence for disease progression of advanced gastric cancer (p. GAST-B, 3 of 6).

The NCCN guideline for Ovarian Cancer Including Fallopian Tumor Cancer and Primary Peritoneal Cancer (3.2024) recommends that patients with recurrent disease undergo comprehensive tumor molecular analysis to identify alterations that would be amenable to targeted therapeutics that have tumor specific or tumor-agnostic benefit (p OV-6). These guidelines also recommend that molecular testing be performed on the most recent tumor tissue available (p. OV-B, 1 of 3).

The NCCN guideline for Pancreatic Adenocarcinoma (1.2025) recommends tumor/somatic molecular profiling to identify targetable alterations for patients with locally advanced or metastatic disease and recommends consideration of this testing for patients with resectable or borderline resectable disease who are candidates for systemic therapy. Testing can include but is not limited to fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations (*BRAF, BRCA1/2*, *KRAS*, *PALB2)*, amplifications (*HER2*), MSI, tumor mutational burden and mismatch repair deficiency (p. PANC-1A, PANC-F, 1 of 12).

The NCCN guideline for Prostate Cancer (1.2025) recommends consideration of somatic multigene tumor testing to identify alterations in HRR genes in addition to MSI and TMB testing for patients with metastatic prostate cancer. NCCN recommends consideration of this testing in patients with regional prostate cancer. The guidelines also recommend that repeat tumor profiles can be considered at the time of progression of disease (p. PROS-C, 2 of 2).

The NCCN guideline for Histiocytic Neoplasms (3.2024) recommends molecular mutation profiling in the work-up/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD) for prognostic and treatment information (p. HIST-C, 1 of 5).

The NCCN guideline for Uterine Neoplasms (2.2025) recommends comprehensive molecular profiling in the initial evaluation of uterine neoplasms, including uterine sarcoma (UTSARC-A1 of 8). This can be done on the initial biopsy or the hysterectomy specimen (p. ENDO-A 2 of 4).

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend somatic molecular profiling to identify uncommon and potentially actionable mutations including fusions, amplifications, MSI, dMMR, and TMB for patients with locally advanced or metastatic disease who are candidates for systemic therapy (p. AMP-6).

NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) recommend molecular testing for a suspected or confirmed gastrointestinal stromal tumor when systemic therapy is being considered (p. GIST-1). If testing does not show a KIT or PDGFRA mutation, NGS testing is recommended to look for alternative driver mutations that will identify targeted therapy options (p. GIST-B).

NCCN guidelines for Central Nervous System Cancers (3.2024) recommend next-generation sequencing in the pathologic workup of CNS tumors, since there are now multiple prognostic and diagnostic biomarkers that should be tested to aid in treatment decisions (p. BRAIN-E 2 of 9).

Food and Drug Administration (FDA)

The FoundationOne CDx test has been approved by the FDA as a companion diagnostic test for several therapies, including some that are indicated for early stage non-small cell lung cancer diagnoses.

back to top

Targeted RNA Fusion Panels for Solid Tumors

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Central Nervous System Cancers (3.2024) recommends RNA sequencing to detect fusions in the following genes: *NTRK* and *BRAF* testing in all gliomas including glioblastoma, *BRAF* for diffuse leptomeningeal glioneuronal tumors, high-grade astrocytoma with piloid features (HGAP), or piloid astrocytoma, and *ZFTA* and *YAP1* in ependymomas. Results of this testing inform diagnosis and treatment options. The preferred method is RNA sequencing or other PCR-based breakpoint methods as FISH is unreliable for *BRAF* fusion detection (p. BRAIN-E, 2, 5-6 of 9; GLIO-A 1 of 9).

NCCN guidelines for Non-Small Cell Lung Cancer (3.2025) recommend consideration of RNA-based NGS testing for patients who don't have identifiable driver oncogenes via broad panel testing to maximize detection of fusion events as fusions involving *ROS1*, *MET, NTRK,* and *RET* have better detection using RNA based methods (p. NSCL-H, 2, 4, 5 of 8).

NCCN guidelines for Soft Tissue Sarcoma (4.2024) state that while morphologic diagnosis remains the preferred method of sarcoma diagnosis, molecular genetic testing using NGS based methods including DNA and RNA sequencing is an ancillary approach that can be helpful depending on type of tumor (p. SARC-C, 1-2 of 4). Fusion testing also plays a role in therapy selection (p. SARC-G 1 of 13).

NCCN guidelines for Histiocytic Neoplasms (3.2024) recommends a gene fusion assay in the workup for Langerhans Cell Histiocytosis, (p. LCH-2), Erdheim-Chester Disease, (p. ECD-2) and Rosai-Dorfman Disease (p. RDD-2). RNA-based molecular panels including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements.

NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) state that all GIST without a *KIT* or *PDGFRA* mutation should be tested for alternative driver mutations, specifically *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions, which may be detected by NGS to identify potential targeted treatments (p. GIST-B).

American Society of Clinical Oncology

ASCO wrote a Provisional Clinical Opinion (2022) in which it was stated that:

- In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease (strength of recommendation: strong).
- Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing (strength of recommendation: moderate).

back to top

Broad RNA Fusion Panels for Solid Tumors

None of the National Comprehensive Cancer Network (NCCN) guidelines currently recommend or address performing broad RNA fusion panels as part of evaluation for solid tumors.

back to top

Colorectal Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Colon Cancer (6.2024) recommends all patients with suspected or proven metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF,* preferably as part of an NGS panel (p. COL-B, 4 of 10). This testing can be performed on the primary colorectal cancers and/or the metastasis.

back to top

Lung Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Non-Small Cell Lung Cancer (3.2025) recommends molecular testing for patients with advanced or metastatic disease and when feasible, testing should be performed via a broad, panel-based approach, most typically performed by NGS. This can be a single assay or a combination of assays and tiered approaches are also acceptable (p. NSCL-19).

Additionally, patients with stages IB-IIIA or IIIB[T3,N2] are recommended to have testing for PD-L1, EGFR and ALK if perioperative systemic therapy is being considered (p. NSCL-E, 1 of 6). In some clinical scenarios it is necessary to do rapid testing which can be followed up with broad testing (p. NSCL-H, 1 of 8, NSCL-H 2 of 8).

NCCN discusses re-testing tumor tissue in patients with progression who are receiving targeted therapy. This applies to all molecular targets associated with lung cancer and is warranted given it could aid in treatment decision-making (NSCL-H 7 of 8).

back to top

Cutaneous Melanoma Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Cutaneous Melanoma (1.2025) recommend molecular testing of *BRAF* for stage III disease, and *KIT* for stage IV disease, or clinical recurrence (p. ME-6, ME-9, ME-18, ME-18A, ME-C 4 of 8). NCCN recommends consideration of broader genomic profiling especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial (ME-6A). Single gene or small multigene panels are acceptable (p. ME-C, 3 of 8). Repeat testing using the same approach following recurrent or metastatic disease is unlikely to yield useful results. Additionally, NCCN states the following: "Repeat testing following progression on targeted therapy (*BRAF*- or *KIT*-directed therapy) does not appear to have clinical utility" (p. ME-C 5 of 8).

back to top

Tumor Specific *BRAF* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Thyroid Carcinoma (5.2024) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS (THYR-1). The guideline also recommends that individuals with anaplastic thyroid cancer and/or locally recurrent, advanced and/or metastatic papillary, follicular, or oncocytic carcinoma undergo molecular testing including *BRAF, NTRK, ALK,* and *RET* (p. ANAP-1, p. PAP-10, p. FOLL-9, p. ONC-9).

The NCCN guideline for Hairy Cell Leukemia (1.2025) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL [classical hairy cell leukemia] immunophenotype (p. HCL-1).

The NCCN guideline for Cutaneous Melanoma (1.2025) recommends *BRAF* mutation testing in patients with stage IIIB or higher cutaneous melanoma if adjuvant therapy or clinical trials are being considered (p. ME-4) and recommends consideration of testing of stage IIIA cutaneous melanoma, especially if *BRAF*-directed therapy is a future treatment option (p. ME-5, ME-5A).

The NCCN guideline on Central Nervous System Cancers (3.2024) recommends *BRAF* fusion and/or mutation testing in patients with gliomas to help characterize the tumor and guide treatment decisions (p. BRAIN-E, 5 of 9).

The NCCN guidelines for Non-Small Cell Lung Cancer (3.2025) recommend molecular testing, including *BRAF* analysis, for advanced or metastatic adenocarcinoma, large cell, NSCLC not otherwise specified, or squamous cell carcinoma and consideration of molecular testing for squamous cell carcinoma of the lung (p. NSCL-19).

The NCCN guidelines for Colon Cancer (6.2024) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma (p. COL-2).

NCCN guidelines for Histiocytic Neoplasms (3.2024) recommends *BRAF* V600E testing (IHC or PCR) from biopsy tissue during the workup for Langerhans cell histiocytosis or Erdheim-Chester disease (p. LCH-2, ECD-2).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommends consideration of *BRAF* testing for all stages of pancreatic cancer when systemic therapy is being considered (p. PANC-F, 1 of 12), including locally advanced/metastatic disease (p. PANC-1A).

NCCN guidelines for Small Bowel Adenocarcinoma (2.2025) recommend *BRAF* V600E testing for metastatic adenocarcinoma (p. SBA-5).

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (5.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer and lists *BRAF* V600E mutation as a targeted biomarker (p. ESOPH-B, 3 and 5 of 6).

NCCN guidelines for Gastric Cancer (5.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic gastric cancer and lists *BRAF* V600E mutation as a targeted biomarker (p. GAST-B, 3 and 5 of 6).

back to top

Tumor Specific BRCA1/2 Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2024) recommends that all patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should have somatic testing of *BRCA1* and *BRCA2* if not previously done to inform maintenance therapy (p. OV-1).

The NCCN guideline on Prostate Cancer (1.2025) recommends tumor testing for *BRCA1* and *BRCA2* (among other HRR genes) in patients with metastatic prostate cancer and consideration of testing in patients with regional or castration sensitive metastatic prostate cancer (p. PROS-C, 2 of 2).

The NCCN guideline on Pancreatic Adenocarcinoma (1.2025) recommends molecular profiling of tumor tissue for patients with resectable, borderline resectable, or locally advanced/metastatic disease who are candidates for systemic therapy. Testing can include but not be limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), etc. (p. PANC-1 and PANC-1A, p. PANC-F, 1 of 12).

American Society of Clinical Oncology (ASCO)

ASCO (2020) published recommendations in an article called “Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer”. The guideline includes a recommendation for somatic *BRCA1* and *BRCA2* tumor testing in women who are negative for germline *BRCA1/2* mutations in order to offer FDA approved treatments (i.e., PARP inhibitors) specific to *BRCA1/2* pathogenic or likely pathogenic variants (p. 1223).

back to top

Tumor Specific *EGFR* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Non-Small Cell Lung Cancer (3.2025) recommend that molecular testing for *EGFR* mutations should be performed when neoadjuvant TKI therapy or nivolumab is a consideration for NSCLC stage IB–IIIA, IIIB [T3,N2] (p. NSCL-E, 1 of 6, NSCL-E 2 of 6, and NSCL-H 3 of 8). Testing should also be performed for advanced or metastatic disease specifically for

patients with advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified (p. NSCL-19).

back to top

Tumor Specific *ESR1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (6.2024) recommend *ESR1* testing for HR-positive/HER2 negative breast cancer in "postmenopausal or premenopausal patients receiving ovarian ablation or suppression or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor" (p. BINV-Q 6 of 14). Testing for *ESR1* mutations should occur at progression following the endocrine therapy (p. BINV-Q 6 of 14).

back to top

Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) recommends FOLR1 testing for recurrent, platinum-resistant disease in order to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit (p. OV-6, LCOC-7, OV-B 1 of 3).

back to top

Tumor Specific IDH1 and IDH2 Variant Analysis (Solid Tumor)

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Central Nervous System Cancers (3.2024) recommends *IDH* mutation testing (*IDH1* and *IDH2*) in the work-up for all gliomas (p. BRAIN-E 2 of 9). Additionally, NCCN lists a preferred systemic treatment option (Vorasidenib) for individuals with astrocytoma who are *IDH*-mutant (p. GLIO-A 4 of 9).

back to top

Tumor Specific *KIT* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Cutaneous Melanoma (1.2025) recommends testing for *KIT* gene mutations in patients with stage IV melanoma as this could impact treatment options (p. ME-9). Molecular testing should be done to confirm *KIT* IHC results (p. ME-C, 3 of 8). NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) recommend *KIT* mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor, especially if tyrosine kinase inhibitors (TKIs) are being considered (p. GIST-1 and GIST-B).

The NCCN guidelines on Acute Myeloid Leukemia (1.2025) recommend molecular testing during the evaluation for AML for genes associated with prognosis or treatment options, including c-KIT analysis (p. EVAL-1, EVAL-2A).

The NCCN guidelines for Systemic Mastocytosis (3.2024) recommends that all patients presenting with signs or symptoms of mastocytosis undergo molecular testing for *KIT* mutations (specifically, the *KIT* D816V mutation) (p. SM-1).

back to top

Tumor Specific *KRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (6.2024) recommends that all patients with suspected or proven metastatic colorectal cancer have tumor testing for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel as this can inform treatment. Testing can be done on the primary tumor or the metastasis (p. COL-2 and COL-B 4 of 10).

The NCCN guideline on Non-Small Cell Lung Cancer (3.2025) recommends molecular testing, including *KRAS,* for patients with advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified and recommends consideration of molecular testing for squamous cell carcinoma of the lung. Testing should be done via broader molecular profiling but concurrent or sequential testing is acceptable (p. NSCL- 19).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) indicate that testing for potentially actionable somatic findings including *KRAS* should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

NCCN guidelines for Biliary Tract Cancers (6.2024) recommend molecular testing for *KRAS* variant G12C in unresectable or metastatic biliary tract cancers including gallbladder, intrahepatic cholangiocarcinoma, or extrahepatic cholangiocarcinoma (p. BIL-B, 2 of 8).

back to top

Tumor Specific *MGMT* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Central Nervous System Cancers (3.2024) recommends *MGMT* promoter methylation testing for all high-grade gliomas (grade 3 and 4). *MGMT* promoter methylation is used for risk stratification in clinical trials and can be helpful with treatment decisions for older adults (specifically, TMZ treatment in non-methylated *MGMT* glioblastoma is not as beneficial) (p. BRAIN-E, 3 of 9).

back to top

Tumor Specific *MLH1* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (6.2024) recommends *MLH1* promoter methylation in all newly diagnosed colon tumors if *MLH1* is abnormal on immunohistochemistry (IHC) (i.e., there is loss of staining of *MLH1* protein) (p. COL-B 4 of 10).

The NCCN guideline on Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025) recommends tumor testing for *MLH1* methylation in patients with colorectal or endometrial (uterine) cancer with tumors that show abnormal *MLH1* IHC. Hypermethylation of the *MLH1* promoter in these tumors has been associated with sporadic cancer, and not Lynch syndrome. If germline testing is done and is negative for Lynch syndrome pathogenic mutations, tumor *MLH1* methylation testing is recommended (p. LS-A 2 of 9).

back to top

Tumor Specific Microsatellite Instability (MSI) Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Colon Cancer (6.2024) recommend determination of tumor MMR or MSI in all individuals with newly diagnosed colorectal cancer (p. COL-B 4 of 10).

The NCCN guidelines for Uterine Neoplasms (2.2025) recommend MSI (among other studies) for patients undergoing initial evaluation for known or suspected uterine malignancy (p. UN-1, ENDO-A 2 of 4, UTSARC-A 1 of 8).

The NCCN guideline on Gastric Cancer (5.2024) recommends MSI testing for all newly diagnosed gastric cancers (p. GAST-1).

The NCCN guideline on Esophageal and Esophagogastric Junction Cancer (5.2024) recommends MSI by PCR or NGS for all patients with newly diagnosed esophageal and EGJ cancers (p. ESOPH-1).

The NCCN guidelines for Cervical Cancer (1.2025) recommend MSI testing for patients with progressive, recurrent, or metastatic cervical carcinoma (p. CERV-A 1 of 7).

The NCCN guideline for Testicular Cancer (1.2025) recommends MSI testing in individuals with pure seminoma or nonseminoma testicular cancer who have had progression after high-dose chemotherapy or third line therapy (p. SEM-7, NSEM-10).

The NCCN guidelines for Biliary Tract Cancers (6.2024) recommends MSI testing for unresectable or metastatic gallbladder cancer or unresectable or metastatic intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma (p. BIL-B, 2 of 8).

The NCCN guidelines for Breast Cancer (6.2024) recommend MSI testing for patients with recurrent unresectable or metastatic breast cancer considering a targeted therapy (p. BINV-Q, 6 of 14).

The NCCN guidelines for Small Bowel Adenocarcinoma (2.2025) recommend universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma (p. SBA-B).

The NCCN guidelines for an Occult Primary (2.2025) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology (p. OCC-1).

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommend MSI (among other studies) for patients with metastatic pancreatic cancer (p. PANC-1A) or resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12).

NCCN guidelines for Vulvar Cancer (4.2024) recommend consideration of MSI testing for recurrent, progressive or metastatic squamous cell carcinoma of the vulva (p. VULVA-A, 2 of 4).

NCCN guidelines for Bone Cancer (1.2025) recommend consideration of testing for TMB and MMR/MSI to inform treatment options for metastatic chondrosarcoma, (p. CHON-4), metastatic chordoma (p. CHOR-3), widely metastatic Ewing sarcoma (p. EW-3), and metastatic osteosarcoma (p. OSTEO-3).

NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of MSI testing for recurrent or metastatic vaginal cancer (p. VAG-5-6, VAG-A 2 of 2).

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) recommend MSI testing as part of the molecular tumor workup for recurrent primary ovarian cancer at any stage (p. OV-6, p. OV-B 1 of 3).

back to top

Tumor Specific *NRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (6.2024) recommends that all patients with metastatic colorectal cancer should have tumor testing for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Testing can be done on the primary tumor or the metastasis (p. COL-B 4 of 10).

back to top

Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Gastric Cancer guidelines (5.2024) recommends PD-L1 testing during the workup for documented or suspected metastatic adenocarcinoma (p. GAST-1).

The NCCN Head and Neck Cancers guidelines (2.2025) state recommendations for first line therapy which could include PD-L1 inhibitors for recurrent, unresectable, oligometastatic, or metastatic cancer of the nasopharynx (p. NASO-B 1 of 3).

The NCCN Bladder Cancer guidelines (6.2024) states recommendations for specific therapies for individuals with locally advanced or metastatic (stage IV) bladder cancer, which can include PD-L1 inhibitors (p. BL-G 2 of 7).

The NCCN Vulvar Cancer guidelines (4.2024) recommends consideration of PD-L1 testing for individuals with recurrent, progressive, or metastatic squamous cell carcinoma of the vulva (p. VULVA-A 2 of 4).

The NCCN Esophageal and Esophagogastric Junction Cancers guidelines (5.2024) recommends PD-L1 testing for individuals during the workup phase for documented or suspected metastatic esophageal and esophagogastric junction cancers (p. ESOPH-1).

The NCCN Cervical Cancer guidelines (1.2025) recommends PD-L1 testing for individuals with recurrent, progressive, or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma (p. CERV-A 1 of 7).

NCCN Non-Small Cell Lung Cancer guidelines (3.2025) recommend PD-L1 testing in patients with stage IB-IIIA, IIIB [T3, N2] non-small cell lung cancer perioperatively (p. NSCL-E, 1 of 5) or for advanced or metastatic adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified (NOS) (p. NSCL-19).

The NCCN Breast Cancer guidelines (6.2024) states recommendations for treatments for recurrent unresectable or stage IV triple negative breast cancer based on PD-L1 tumor status (p. BINV-Q 2 of 14).

NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of PD-L1 testing for recurrent or metastatic vaginal cancer (p. VAG-5, VAG-6, VAG-A 2 of 2).

Food and Drug Administration (FDA)

The FDA's list of cleared or approved companion diagnostic devices lists several cancer types approved for testing via the immunohistochemistry assay for PD-L1 for the purposes of treatment decision-making. These cancer types include, in part: head and neck squamous cell carcinoma, urothelial carcinoma (PMA number 150013, supplement number S014), and triple negative breast cancer (PMA number 150013, supplement S020).

back to top

Tumor Specific *PIK3CA* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (6.2024) recommends molecular testing for *PIK3CA* mutations in patients with recurrent unresectable or stage IV HR-positive/HER2-negative breast cancers (p. BINV-Q, 6 of 15) to identify candidates for FDA-approved therapies.

The NCCN guidelines for Head and Neck Cancers (2.2025) include *PIK3CA* in a list of recommended NGS profiling biomarker testing that should be done prior to treatment for metastatic salivary gland tumors (p. SALI-4).

back to top

Tumor Mutational Burden (TMB)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Breast Cancer (6.2024) recommend tumor mutation burden (TMB) testing for patients with recurrent unresectable or stage IV disease for whom pembrolizumab is being considered for treatment (p. BINV-Q, 7 of 15).

The NCCN guidelines for Biliary Tract Cancers (6.2024) recommend tumor mutational burden testing for unresectable or metastatic gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma (p. BIL-B, 2 of 8).

The NCCN guidelines for Occult Primary Cancers (2.2025) recommends tumor mutational burden testing for patients with suspected metastatic malignancy of uncertain pathology (p. OCC-1).

The NCCN guidelines for Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2024) recommend tumor analysis, including tumor mutational burden, for recurrent ovarian/fallopian tube/primary peritoneal cancer (p. OV-B 1 of 3).

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommend testing of tumor mutational burden for patients with resectable, borderline resectable, or locally advanced and metastatic pancreatic cancer who are candidates for systemic therapy (p. PANC-1, PANC-1A, PANC-F, 1 of 12).

The NCCN guidelines for Prostate Cancer (1.2025) recommend somatic testing for tumor mutational burden for patients with metastatic castration-resistant prostate cancer (p. PROS-15).

The NCCN guidelines for Testicular Cancer (1.2025) recommend tumor mutational burden testing for patients with pure seminoma or nonseminoma testicular cancer who have experienced disease progression after high-dose chemotherapy or third-line therapy (p. SEM-7, NSEM-10).

The NCCN guidelines for Uterine Neoplasms (2.2025) recommend consideration of tumor mutational burden testing for patients with endometrial cancer (p. ENDO-A 2 of 4). The guidelines also recommend tumor mutational burden testing be done for patients with uterine sarcoma (p. UTSARC-A 1 of 8).

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommends consideration of tumor/somatic molecular profiling, including tumor mutational burden, for patients with locally advanced/metastatic disease who are candidates for systemic therapy (p. AMP-3).

NCCN guidelines for Bone Cancer (1.2025) recommend consideration of testing for TMB and MMR/MSI to inform treatment options for metastatic chondrosarcoma, (p. CHON-4), metastatic chordoma (p. CHOR-3), widely metastatic Ewing sarcoma (p. EW-3), and metastatic osteosarcoma (p. OSTEO-3).

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (5.2024) recommends consideration of molecular testing (IHC, FISH, PCR, NGS) for identification of biomarkers for which targeted therapies are approved. Tumor mutational burden is a biomarker for which testing should be done (p. ESOPH-B, 5 of 6).

NCCN guidelines for Gastric Cancer (5.2024) recommends consideration of genomic profiling, including tumor mutational burden, for individuals with unresectable, locally advanced, recurrent or metastatic gastric cancer (p. GAST-B, 5 of 6 and GAST-F 5 of 20).

NCCN guidelines for Head and Neck Cancers (2.2025) recommends that NGS profiling and other appropriate biomarker testing should be done to assess tumor mutational burden (TMB), among other biomarkers, prior to treatment for metastatic salivary gland tumors (p. SALI-4).

NCCN guidelines for Neuroendocrine and Adrenal Tumors (4.2024) recommends consideration of TMB testing for locally advanced unresectable or metastatic, extra pulmonary poorly differentiated neuroendocrine carcinoma, large or small cell carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm (p. PDNEC-1A) and recommends consideration of TMB testing for adrenocortical carcinoma (p. AGT-5).

NCCN guidelines for Thyroid Carcinoma (5.2024) recommends consideration of tumor mutational burden for patients with locally recurrent, advanced and/or metastatic papillary (p. PAP-10), follicular (p. FOLL-9) or oncocytic carcinoma (p. ONC-9) that is not amenable to RAI therapy, and for patients with stage IVC anaplastic carcinoma (p. ANAP-3).

NCCN guidelines for Vulvar Cancer (4.2024) recommend consideration of tumor mutational burden (TMB) testing in the pathologic assessment for squamous cell carcinoma of the vulva (p. VULVA-A, 2 of 4).

NCCN guidelines for Small Bowel Adenocarcinoma (2.2025) recommend consideration of tumor mutational burden testing for metastatic adenocarcinoma (p. SBA-5).

NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of tumor mutational burden testing for recurrent or metastatic squamous cell carcinoma/adenocarcinoma of the vagina to help guide systemic treatment options (p. VAG-D 1 of 2, VAG-A 2 of 2).

Food and Drug Administration (FDA)

Per the FDA label for KEYTRUDA (pembrolizumab) injection, TMB is included as part of the indications and usage for the drug:

"Tumor Mutational Burden-High (TMB-H) Cancer for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established."

back to top

Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Minimal Residual Disease Testing for Cancer" states the following regarding the use of minimally invasive molecular DNA and RNA tests that detect minimal residual disease (MRD) in patients with a personal history of cancer:

1. The patient has a personal history of cancer, the type and staging of which is within the intended use of the MRD test;

2. The identification of recurrence or progression of disease within the intended use population of the test is identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management;

3. The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard-of-care for monitoring a given cancer type) of recurrence or progression.

"When the patient is NOT known to have cancer (specifically when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer), a second kind of test may exist wherein a single timepoint may constitute a single test. In such patients, the frequency of MRD testing is in accordance with national or society guidelines or recommendations."

From the billing and coding article:

"Intended uses that have met clinical validity (CV) criteria under the policy include: (1) the diagnosis of disease progression, recurrence, or relapse for advanced colorectal (Natera and

Guardant), muscle-invasive bladder, ovarian, and (neoadjuvant) breast cancers (Natera)....(3) the monitoring of response to immune-checkpoint inhibitor therapy for colorectal cancer (Guardant) or any solid tumor (Natera). However, the tests listed in the table may have only been approved for one or more (but not necessarily all) of these indications.

"Regarding the use of NGS-based MRD tests (i.e., Signatera) in patients with cancer– The service may be performed once per patient per cancer diagnosis, unless there is clinical evidence of *a priori* change in genetic content."

Concert Note:

For use of minimal residual disease testing, absent clear, specific and evidence-based guideline recommendations for a particular regimen of testing, a default frequency of once per cancer diagnosis for patients with cancer or once every 12 months for patients without cancer will be adopted.

back to top

Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

back to top

HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Minimal Residual Disease Testing for Cancer" states the following regarding the necessity of minimally invasive molecular DNA and RNA tests that detect minimal residual disease (MRD) in patients with a personal history of cancer:

- The patient has a personal history of cancer, the type and staging of which is within the intended use of the MRD test;
- The identification of recurrence or progression of disease within the intended use population of the test is identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management;
- The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard-of-care for monitoring a given cancer type) of recurrence or progression;

When the patient is NOT known to have cancer (specifically when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and

subsequently the patient is no longer being subjected to therapeutic interventions for cancer), a second kind of test may exist wherein a single timepoint may constitute a single test. In such patients, the frequency of MRD testing is in accordance with national or society guidelines or recommendations."

From the billing and coding article:

"Intended uses that have met clinical validity (CV) criteria under the policy include: … (2) the diagnosis of disease recurrence or relapse for advanced breast (RaDaR) and HPV-driven oropharyngeal cancer (Naveris).... However, the tests listed in the table may have only been approved for one or more (but not necessarily all) of these indications."

Concert Note

For use of minimal residual disease testing, absent clear, specific and evidence-based guideline recommendations for a particular regimen of testing, a default frequency of once per cancer diagnosis for patients with cancer or once every 12 months for patients without cancer will be adopted.

back to top

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

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer guidelines (1.2025) recommend 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 (5.2024) recommend 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 (p. GAST-B 5 of 6).

NCCN Pancreatic Adenocarcinoma guidelines (1.2025) recommend tumor molecular profiling for patients with locally advanced, metastatic disease, recurrence after resection, or disease progression 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-1, PANC-1A, PANC-5, PANC-9, PANC-10, PANC-11).

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (5.2024) recommend consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced cancer who may be unable to safely undergo a traditional biopsy (p. ESOPH-B 5 of 6).

NCCN Colon Cancer guidelines (6.2024) 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 (3.2025) recommend broad-based molecular profiling using ctDNA only when disease is advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified (NOS). NCCN also recommends consideration of broad molecular profiling for advanced or metastatic squamous cell carcinoma (p. NSCL-19). Per NCCN, "[c]omplete genotyping for *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET*, and *ERBB2 (HER2)* via biopsy and/or plasma testing" are recommended either on tissue, plasma, or both (p. NSCL-20). 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 (1.2025) support the use of cell-free circulating tumor DNA (ctDNA) if tumor tissue is unavailable (p. ME-C 3 of 8). In individuals with initial presentation in stage IV disease, broad genomic profiling using larger NGS panels is recommended if feasible, "especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial" (ME-C 4 of 8). If *BRAF* single-gene testing was already done and was negative, NCCN recommends consideration of a larger profiling panel to identify other potential biomarkers (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 (1.2025) 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 (6.2024) 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 (3.2024) 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 (4.2024) recommends consideration of 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-1, PDNEC-1A).

NCCN Occult Primary guidelines (2.2025) 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-1, 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 (6.2024) 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).

back to top

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

National Comprehensive Cancer Network (NCCN)

The NCCN Non-Small Cell Lung Cancer guidelines (3.2025) recommend biomarker testing be performed pre-treatment for patients with clinically confirmed 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-14, NSCL-15, NSCL-19, NSCL-H 2-7 of 8). Broad NGS panel-based testing is recommended over other modalities and smaller tests where feasible (NSCL-H, 2 of 8). 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, however ctDNA should not be used outside of advanced or metastatic disease (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).

back to top

***EGFR* Variant Analysis via ctDNA**

National Comprehensive Cancer Network (NCCN)

The NCCN Non-Small Cell Lung Cancer guidelines (3.2025) 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).

back to top

BRAF Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (6.2024) 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 (1.2025) 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 (1.2025) 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).

back to top

KRAS Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Colon Cancer guidelines (6.2024) recommend tumor molecular testing for *KRAS, NRAS*, and *BRAF* mutations in all patients with metastatic colorectal cancer. This analysis can be done individually, although performing it as part of an NGS panel is preferred. 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 (1.2025) 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).

back to top

PIK3CA Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (6.2024) recommend *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 15).

back to top

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."

back to top

Circulating Tumor Cell (CTC) Enumeration

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (6.2024) 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-77).

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."

back to top

Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests

National Comprehensive Cancer Network (NCCN)

The NCCN Thyroid Carcinoma guidelines (5.2024) recommend that individuals with anaplastic thyroid cancer should undergo molecular testing including *ALK* (p. ANAP-1). *ALK* testing is also recommended for locally recurrent, advanced, and/or metastatic papillary thyroid carcinoma (p. PAP-10) and locally recurrent, advanced, and/or metastatic follicular thyroid carcinoma (p. FOLL-9).

NCCN Non-Small Cell Lung Cancer guidelines (3.2025) recommend *ALK* rearrangement testing in patients with Stage IB-IIIA, IIIB [T3,N2] disease perioperatively for consideration of systemic therapy (p. NSCL-E, 1 of 6) as well as for patients with advanced or metastatic adenocarcinoma, large cell, squamous cell, or NSCLC not otherwise specified (NOS) (p. NSCL-19).

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend somatic molecular profiling for patients with locally advanced/metastatic disease if systemic therapy is being considered. Potentially actionable somatic findings include fusions involving the ALK gene (p. AMP-3).

NCCN guidelines for Histiocytic Neoplasms (3.2024) recommends molecular testing of a tissue biopsy during the diagnostic workup for Langerhans cell histiocytosis and Erdheim-Chester disease, and suggests RNA based molecular panel including fusion testing for *ALK*; however if *ALK* rearrangement is suspected clinically, or if fusion panel testing is not available, ALK immunohistochemistry and FISH studies may be performed (p. LCH-2, ECD-2).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommend somatic molecular profiling for patients with locally advanced/metastatic disease as well as those with resectable or borderline

resectable disease if systemic therapy is being considered. Potentially actionable somatic findings include fusions involving the ALK gene (p. PANC-1A).

NCCN guidelines for Pediatric Central Nervous System Cancers (2.2025) recommend broad molecular testing to classify pediatric diffuse high-grade gliomas. This includes detection of fusions involving the ALK gene (p. PGLIO-B, 2 of 4).

back to top

Bladder Cancer Diagnostic and Recurrence FISH Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled “Lab: Bladder/Urothelial Tumor Markers” includes the following utilization guidelines for bladder marker testing.

Regarding the UroVysion Bladder Cancer Kit: “It is used to detect chromosomal abnormalities in voided urine to assist not only in bladder cancer surveillance but also in the initial identification of bladder cancer.”

“*Follow-up after initial diagnosis/most recent occurrence and treatment*

- Maximum of 4 bladder tumor marker studies per year for years 1-2
- Maximum of 3 bladder tumor marker studies per year for year 3
- Maximum of 2 bladder tumor marker studies for year 4 and
- Maximum of 1 bladder tumor marker studies follow-up annually for up to 15 years.”

“For high risk patients with persistent hematuria and a negative FISH assay following a comprehensive diagnostic (no tumor identified) workup, ONE repeat FISH testing in conjunction with cystoscopy is considered reasonable and necessary within 1 year of the original attempted diagnosis.”

The CMS LCD Reference Article “Billing and Coding: Lab: Bladder/Urothelial Tumor Markers” states the following: “This A/B MAC will only cover bladder tumor marker fluorescence in situ hybridization (FISH) testing services when performed using validated assays. To date, UroVysion Bladder Cancer Kit is the only Federal Drug Administration (FDA) approved assay that is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus via FISH.

Bladder cancer tumor markers performed by any technology, immunoassay, molecular or FISH testing, are not covered for screening of all patients with hematuria.”

back to top

Tumor Specific *ERBB2* (*HER2*) Deletion/Duplication (IHC, FISH and CISH)

National Comprehensive Cancer Network (NCCN)

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (5.2024) recommend HER2/*ERBB2* testing using FISH or IHC for patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma if trastuzumab is being considered for treatment (p. ESOPH-B, 3 of 6).

NCCN Head and Neck Cancers guidelines (2.2025) recommend HER2/*ERBB2* testing prior to treatment for individuals diagnosed with recurrent, unresectable, or metastatic salivary gland tumors (p. SALI-4).

NCCN Colon Cancer guidelines (6.2024) recommend HER2/*ERBB2* testing during the workup for suspected or proven metastatic colorectal cancer (p. COL-2). These guidelines also recommend consideration of HER2 analysis for metastatic appendiceal adenocarcinoma (p. COL-I 2 of 3).

NCCN Gastric Cancer guidelines (5.2024) recommend HER2/*ERBB2* testing for patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach if trastuzumab is being considered (p. GAST-B, 3 of 6).

NCCN Breast Cancer guidelines (6.2024) recommend HER2/*ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer (p. BINV-A 1 of 2).

NCCN Cervical Cancer guidelines (1.2025) recommend HER2 testing for recurrent, advanced or metastatic cervical carcinoma (p. CERV-A 1 of 7).

NCCN Uterine Neoplasms guidelines (2.2025) recommend HER2 IHC with reflex to FISH for all serous and carcinosarcoma endometrial tumors and recommends consideration of HER2 testing for all tumors that have abnormal p53 by IHC (p. ENDO-A, 1 of 4).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommend consideration of HER2 amplification testing for patients with locally advanced or metastatic disease (p. PANC-5), recurrence after resection (p. PANC-9), and with resectable or borderline resectable disease being considered for neoadjuvant systemic therapy (p. PANC-F, 1 of 12).

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) recommend HER2 testing by IHC for recurrent disease after primary treatment (p. OV-6).

NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of HER2 testing by IHC or FISH for recurrent or metastatic vaginal cancer (p. VAG-5, VAG-6, VAG-A 2 of 2).

NCCN guidelines for Bladder Cancer (6.2024) recommend consideration of IHC for HER2 overexpression for stage IIIB or higher muscle invasive bladder cancer (p. BL-8 through BL-10).

NCCN guidelines for Small Bowel Adenocarcinoma (2.2025) recommend testing for HER2 amplifications for patients with metastatic disease (p. SBA-5).

back to top

NTRK Fusion Analysis Panel

National Comprehensive Cancer Network (NCCN)

The NCCN Thyroid Carcinoma guidelines (5.2024) recommend that individuals with anaplastic thyroid cancer (p. ANAP-1) or locally recurrent, advanced, and/or metastatic papillary, follicular, and oncocytic carcinoma (formerly called Hurthle cell carcinoma) undergo molecular testing including *NTRK* as part of disease workup (p. PAP-10, p. FOLL-9, p. ONC-9).

The NCCN Colon Cancer Guidelines (6.2024) recommend broad molecular profiling to, including *NTRK*, for patients with suspected or proven metastatic adenocarcinoma (p. COL-2). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. COL-D 2 of 11).

The NCCN Non-Small Cell Lung Cancer guidelines (3.2025) recommends *NTRK* molecular analysis for patients with advanced or metastatic adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NOS) and recommends consideration of *NTRK* testing for advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-19). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. NSCL-33).

The NCCN Occult Primary guidelines (2.2025) states that patients with metastatic or unresectable *NTRK* gene fusion positive adenocarcinomas without a known acquired resistance mutation, who have no satisfactory treatment options or who have progressed on treatment can be treated with entrectinib and/or larotrectinib or repotrectinib (p. OCC-B, 8 of 14).

The NCCN Cervical Cancer guidelines (1.2025) recommends *NTRK* fusion analysis for patients with cervical sarcoma (p. CERV-A 1 of 7).

The NCCN Vulvar Cancer guidelines (4.2024) recommends consideration of *NTRK* fusion analysis for recurrent, progressive, or metastatic squamous cell carcinoma of the vulva (p. VULVA-A 2 of 4).

The NCCN Uterine Neoplasms guidelines (2.2025) recommends consideration of *NTRK* fusion analysis for recurrent or metastatic endometrial carcinoma (p. ENDO-A 2 of 4) or metastatic uterine sarcoma (p. UTSARC-A 1 of 8).

The NCCN Breast Cancer guidelines (6.2024) recommend *NTRK* fusion testing for recurrent unresectable or stage IV disease if eligible for larotrectinib, entrectinib or repotrectinib treatment (no known resistance mutation and no satisfactory alternatives or have progressed on treatment) (p. BINV-Q 7 of 14).

The NCCN Gastric Cancer guidelines (5.2024) recommends consideration of comprehensive genomic profiling including *NTRK* fusion analysis for unresectable locally advanced, recurrent, or metastatic gastric cancer (p. GAST-B 5 of 6, GAST-F 5 of 20).

The NCCN Esophageal and Esophagogastric Junction Cancer guidelines (5.2024) recommends consideration of comprehensive genomic profiling including *NTRK* fusion analysis for unresectable, locally advanced, recurrent, or metastatic esophageal cancer (p. ESOPH-B 5 of 6). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. ESOPH-F 6 of 22).

The NCCN Acute Lymphoblastic Leukemia guidelines (3.2024) and Pediatric Acute Lymphoblastic Leukemia guidelines (2.2025) recommend *NTRK* fusion analysis for acute lymphoblastic leukemia (ALL) for the purposes of risk stratification (p. ALL-3; p. PEDALL-B).

The NCCN Soft Tissue Sarcoma guidelines (4.2024) recommend larotrectinib, entrectinib or repotrectinib for patients with advanced or metastatic disease and *NTRK* gene fusion-positive tumors (p. SARC-G 1 of 13).

The NCCN Neuroendocrine and Adrenal Tumors guidelines (4.2024) recommends consideration of *NTRK* fusion testing for patients with unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm (p. PDNEC-1, PDNEC-1A). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. NE-H 5 of 9).

The NCCN Head and Neck Cancers guidelines (2.2025) recommend use of NGS profiling and other appropriate biomarker testing to evaluate *NTRK* prior to treatment for metastatic salivary gland tumors (p. SALI-4).

The NCCN Hepatocellular Carcinoma guidelines (2.2024) indicate that larotrectinib, entrectinib, and repotrectinib are options for treatment in patients with *NTRK* gene fusion positive tumors (p. HCC-I, 1 of 2).

The NCCN Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer guidelines (3.2024) recommend tumor molecular testing including *NTRK* testing for recurrent disease if prior testing for these markers was not done (p. OV-6). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. OV-C 8 of 12).

The NCCN Small Bowel Adenocarcinoma guidelines (2.2025) recommends larotrectinib and entrectinib as options for subsequent-line treatment of metastatic small bowel adenocarcinoma that is *NTRK* gene fusion positive (p. SBA-D 1 of 7).

The NCCN Pediatric Central Nervous System Cancers guidelines (2.2025) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including NGS with fusion detection for *NTRK1/2/3*, (p. PGLIO-B, 2 of 4).

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommend testing for potentially actionable somatic findings including *NTRK* fusions for patients with locally advanced/metastatic disease (p. PANC-1 and PANC-1A). In addition, patients with resectable or borderline resectable disease who are considering systemic therapy are recommended to consider testing for somatic findings including *NTRK* fusions (p. PANC-F, 1 of 12). For individuals who are *NTRK* gene fusion-positive, NCCN lists the following biomarker-directed therapies: entrectinib, larotrectinib, and repotrectinib (p. PANC-F 3 of 12).

The NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of *NTRK* fusion testing for recurrent or metastatic vaginal cancer (p. VAG-5, VAG-6, VAG-A 2 of 2).

The NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) lists the following biomarker-directed therapies for individuals with unresectable, progressive or metastatic disease: entrectinib, larotrectinib, and repotrectinib (p. GIST-E 1 of 4, GIST-E 2 of 4).

Food and Drug Administration

The FDA label for Augtyro (repotrectinib) includes indications and usage information for the treatment of the following:

- “adult patients with locally advanced or metastatic ROS1-positive nonsmall cell lung cancer (NSCLC) (1.1).
- adult and pediatric patients 12 years of age and older with solid tumors that:
    - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and
    - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

have progressed following treatment or have no satisfactory alternative therapy.

back to top

Tumor Specific *RET* Gene Rearrangement Tests (FISH)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Thyroid Carcinoma (5.2024) recommend that patients with recurrent or persistent medullary thyroid carcinoma, or patients with symptomatic disease/progression should have somatic *RET* testing if germline wild type or germline unknown (p. MEDU-6 and MEDU-7). The guideline also recommends that individuals with anaplastic thyroid cancer and/or locally recurrent, advanced, and/or metastatic papillary, follicular, or oncocytic carcinoma that cannot be treated with radioactive iodine should undergo molecular testing including *RET* if not previously done (p. ANAP-3, PAP-10, FOLL-9, ONC-9).

The NCCN guideline on Non-Small Cell Lung Cancer (3.2025) recommends analysis for *RET* gene rearrangements in patients with advanced or metastatic adenocarcinoma of the lung, large cell carcinoma of the lung, or NSCLC not otherwise specified and recommends consideration of RET gene testing for patients with advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-19), noting that NGS-based methodology has a high specificity and that RNA-based NGS is preferable to DNA-based NGS for fusion detection (p. NSCL-H, 5 of 8).

The NCCN guideline for Cervical Cancer (1.2025) recommends consideration of *RET* gene fusion testing for patients with locally advanced or metastatic cervical cancer of the following pathologies: squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma (p. CERV-1 and CERV-A, 1 of 7).

NCCN guidelines for Breast Cancer (6.2024) list *RET* fusion as a biomarker with an FDA approved therapy for any subtype of recurrent unresectable or stage IV disease. Either tumor tissue or blood can be used for detection (p. BINV-Q, 6 of 14).

NCCN guidelines for Colon Cancer (6.2024) recommend broad molecular profiling including *RET* fusion detection as part of the workup for suspected or proven metastatic adenocarcinoma (p. COL-2).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommends consideration of testing for somatic mutations including *RET* fusions for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12) and recommends this testing for locally advanced/metastatic disease (p. PANC-1 and PANC-1A).

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (5.2024) recommend consideration of *RET* gene fusion testing for patients with squamous cell carcinoma and locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer (p. ESOPH-B, 5 of 6, ESOPH-10, ESOPH-19).

NCCN guidelines for Gastric Cancer (5.2024) recommend consideration of *RET* gene fusion testing for patients with locally advanced, recurrent or metastatic gastric cancer (p. GAST-B, 5 of 6).

NCCN guidelines for Vaginal Cancer (3.2025) recommend consideration of *RET* fusion testing for recurrent or metastatic vaginal cancer (p. VAG-6 and VAG-A 2 of 2).

back to top

Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN)

NCCN Non-Small Cell Lung Cancer guidelines (3.2025) recommend *ROS1* rearrangement testing in patients with advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, and NSCLC not otherwise specified (NOS) squamous cell carcinoma of the lung (p. NSCL-19). NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend consideration of tumor molecular profiling, including for ROS1 fusions, for patients with locally advanced or metastatic disease who are considering systemic therapy (p. AMP-3).

NCCN guidelines for Pancreatic Adenocarcinoma (1.2025) recommends consideration of tumor molecular profiling including ROS1 fusions for patients with resectable or borderline resectable disease (p. PANC-F, 1 of 12) and recommends this testing for locally advanced or metastatic disease (p. PANC-1A).

NCCN guidelines for Pediatric Central Nervous System Cancers (2.2025) state that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas, including detection of fusions involving *ROS1* (p. PGLIO-B, 2 of 4).

back to top

Cancer Exome and Genome Sequencing

National Comprehensive Cancer Network Biomarker Compendium

None of the National Comprehensive Cancer Network (NCCN) guidelines currently recommend or address performing cancer exome and/or genome sequencing as part of evaluation for cancers or tumors.

back to top

DEFINITIONS

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic)**:** Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.
3. **Circulating Tumor Cells (CTCs)** are intact cells that have shed into the bloodstream or lymphatic system from a primary tumor or a metastasis site, and are carried around the body by blood circulation.
4. **Tumor mutational burden:** A measurement of mutations carried by tumor cells and is a predictive biomarker that is being studied to evaluate its association with response to immunotherapy.

5. **Widely metastatic:** A cancer for which local control cannot be delivered to all areas of disease (per NCCN guidelines).

back to top

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back to top

Medica Central Coverage Policy

Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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