Medica Central Coverage Policy

Policy Name:	**Genetic Testing – Oncology Testing: Solid Tumor Molecular Diagnostics MP9608**
Effective Date:	**01/01/2026**

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 and References 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. Please see the Concert Platform for additional registered tests.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Molecular Profiling Panels			
Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels	FoundationOne CDx - 0037U (Foundation Medicine)	81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0211U, 0244U, 0250U, 0329U, 0334U, 0379U, 0391U, 0473U, 0523U, 0538U, 0543U, C00-D49, Z85	Rationale/ References
	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	SUPPORT
	Strata Select - 0391U (Strata Oncology)		
	oncoReveal CDx - 0523U (Pillar Biosciences, Inc.)		
	PredicineATLAS Assay - 0538U (Predicine)		
	TruSight Oncology Comprehensive - 0543U (Illumina)		
	MI Cancer Seek - NGS Analysis - 0211U (Caris Life Sciences)		
Targeted RNA Fusion Panels for Solid Tumors	Targeted Solid Tumor NGS Fusion Panel (NeoGenomics Laboratories)	81449, C34, C49, C71, C91, C96	Rationale/ References
Broad RNA Fusion Panels for Solid Tumors	Aventa FusionPlus - 0444U (Aventa Genomics)	81455, 81456, 0444U, C00-C80	Rationale/ References
	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	Rationale/ References
	COLONSEQPlus Panel (MedFusion)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test - 0022U (Thermo Fisher Scientific)	81457, 0022U, 0478U, C34	Rationale/ References
	OnkoSight Advanced Lung Cancer NGS Panel (BioReference Laboratories)		
	Lung HDPCR - 0478U (Protean BioDiagnostics)		
Cutaneous Melanoma Focused Molecular Profiling Panels	MelanomaSeqPlus (Quest Diagnostics)	81445, 81457, C43, D03	Rationale/ References
	OnkoSight Advanced Melanoma NGS Panel (BioReference Laboratories)		
Single Gene Testing of Solid Tumors			
Tumor Specific *BRAF* Variant Analysis	BRAF Mutation Analysis (NeoGenomics Laboratories)	81210, C18-C21, C34, C43, C71, C73, C91.4	Rationale/ References
Tumor Specific *BRCA1/2* Variant Analysis	BRCA1/2 Mutation Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81163, 81212, 81216, C56, C61	Rationale/ References
	BRCA1/2 Mutation Analysis for Tumors (NeoGenomics Laboratories)		
Tumor Specific *EGFR* Variant Analysis	EGFR Mutation Analysis by PCR (NeoGenomics Laboratories)	81235, C34	Rationale/ References
Tumor Specific *ESR1* Variant Analysis	ESR1 Mutations Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81479, C50	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Tumor Specific FOLR1 Protein Analysis	FOLR1 Immunohistochemistry Analysis (LabCorp)	88360, C56	Rationale/ References
Tumor Specific *IDH1* and *IDH2* Variant Analysis (Solid Tumor)	IDHNow Mutation Analysis by PCR (NeoGenomics Laboratories)	81120, 81121, 0481U, C71, C92, D49.6	Rationale/ References
	IDH1, IDH2, and TERT Mutation Analysis, Next Generation Sequencing, Tumor (IDTRT) - 0481U (Mayo Clinic)		
Tumor Specific *KIT* Variant Analysis (Solid Tumor)	KIT Mutation Analysis (ProPath)	81272, C43, C49.A, C92, D47.1, D47.02	Rationale/ References
Tumor Specific *KRAS* Variant Analysis	KRAS Mutation Analysis by PCR (NeoGenomics Laboratories)	81275, 81276, C18-21, C34	Rationale/ References
Tumor Specific *MGMT* Methylation Analysis	MGMT Promoter Methylation - Tumor (Ohio State University Molecular Pathology Laboratory)	81287, C71	Rationale/ References
Tumor Specific *MLH1* Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics Laboratories)	81288, C18-C21, C54.1	Rationale/ References
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	Rationale/ References
Tumor Specific *NRAS* Variant Analysis	NRAS Mutation Analysis (NeoGenomics Laboratories)	81311, C18-C21	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
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	Rationale/ References
Tumor Specific *PIK3CA* Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309, 0155U, C50, C55	Rationale/ References
	PIK3CA Mutation Analysis, therascreen - QIAGEN - 0155U (LabCorp)		
Tumor Mutational Burden (TMB) Testing			
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479, C00-D49, Z85	Rationale/ References
Measurable (Minimal) Residual Disease (MRD) Testing			
Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing	Signatera - Residual Disease Test (MRD) - 0340U (Natera)	81479, 0340U, 0356U, 0422U, 0569U, C00-D49, Z85	Rationale/ References
	Guardant Reveal - 0569U (Guardant Health)		
	Guardant360 Response - 0422U (Guardant Health)		
	Oncodetect Molecular Residual Disease Test (Exact Sciences)		
	NavDx - 0356U (Naveris)		
Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing	Colvera - 0229U (Clinical Genomics Pathology, Inc.)	0229U, 0306U, 0307U, 0486U, 0498U, 0501U, 0560U, 0561U, C00-D49, Z85	Rationale/ References
	Invitae PCM Tissue Profiling and MRD Baseline Assay - 0306U (Invitae Corporation)		
	Invitae PCM MRD Monitoring - 0307U (Invitae Corporation)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Northstar Response - 0486U (BillionToOne)		
	OptiSeq Colorectal Cancer NGS Panel - 0498U (DiaCarta, Inc.)		
	QuantiDNA Colorectal Cancer Triage Test - 0501U (DiaCarta, Inc.)		
	Haystack MRD Baseline - 0560U (Quest Diagnostics)		
	Haystack MRD Monitoring - 0561U (Quest Diagnostics)		
HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing	NavDx - 0356U (Naveris)	0356U, 0470U, C10.9	Rationale/ References
	HPV-SEQ Test - 0470U (Sysmex Inostics, Inc.)		
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, 0539U, C15, C16, C18, C25, C34, C61	Rationale/ References
	Guardant360 - 0326U (Guardant Health)		
	Guardant360 CDx - 0242U (Guardant Health)		
	Guardant360 83+ genes (Guardant Health)		
	NeoLAB Solid Tumor Liquid Biopsy (NeoGenomics Laboratories)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus)		
	LiquidHALLMARK - 0409U (Lucence Health)		
	Caris Assure - 0485U (Caris Life Sciences)		
	Northstar Select - 0487U (BillionToOne)		
	OptiSeq Dual Cancer Panel Kit - 0499U (DiaCarta, Inc.)		
	LiquidHALLMARK - 0530U (Lucence Health, Inc.)		
	PredicineCARE Assay - 0539U (Predicine)		
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung - 0179U (Resolution Bioscience, part of Exact Sciences)	81210, 81235, 81275, 81462, 81479, 0179U, 0388U, C34	Rationale/ References
	OncoBEAM Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc.)		
	InVisionFirst-Lung Liquid Biopsy - 0388U (NeoGenomics Laboratories)		
	GeneStrat NGS (Biodesix)		
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)			
EGFR Variant Analysis via ctDNA	EGFR ultrasensitive "liquid biopsy" (Brigham and Women's Hospital -	81235, C34	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Center for Advanced Molecular Diagnostics)		
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600, Blood (Mayo Clinic Laboratories)	81210, C18-C21, C43	Rationale/ References
	BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR (ARUP Laboratories)		
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Clinic Laboratories)	81275, 81276, C18-C20	Rationale/ References
PIK3CA Variant Analysis via ctDNA	therascreen PIK3CA RGQ PCR Kit - 0177U (QIAGEN)	81309, 0177U, C50	Rationale/ References
	Cell-Free DNA PIK3CA Test, Blood (Mayo Clinic Laboratories)		
Circulating Tumor Cell (CTC) Tests			
Circulating Tumor Cell (CTC) Enumeration	CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test - 0337U (Menarini Silicon)	0337U, 0338U, 0490U, 0491U, 0492U, C00.0-C96.9	Rationale/ References
	CELLSEARCH Circulating Multiple Myeloma Cell (CMMC) Test - 0338U (Menarini Silicon)		
	CELLSEARCH Circulating Melanoma Cell (CMC) Test - 0490U (Menarini Silicon)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	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			
Tumor Specific *ALK* Gene Rearrangement (Qualitative FISH and PCR) Tests	ALK FISH, Non-Small-cell Lung Cancer (LabCorp)	88271, 88274, C34, C73	Rationale/ References
Bladder Cancer Diagnostic and Recurrence FISH Tests	UroVysion Bladder Kit (Quest Diagnostics)	88120, 88121, C67, R31.9, Z85, Z85.5	Rationale/ References
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	Rationale/ References
NTRK Fusion Analysis Panel for Solid Tumors	NTRK NGS Fusion Panel (NeoGenomics Laboratories)	81191, 81192, 81193, 81194, C15, C16, C18, C34, C49.9, C50, C51, C53, C54, C73, C80.1, C91	Rationale/ References
Tumor Specific *RET* Gene Rearrangement Tests (FISH)	RET FISH (NeoGenomics Laboratories)	88271, 88275, 88291, 88374, 88377, C34, C53, C73	Rationale/ References
	Oncology FISH Analysis - RET Rearrangement (Baylor Genetics, LLC)		
Tumor Specific *ROS1* Gene Rearrangement	FISH ROS1 Rearrangement (Johns Hopkins Medical Institutions-Pathology Laboratory)	88271, 88274, 88342, 88366, C34	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
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	Rationale/ References
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)		
	Tempus xE (Tempus)		

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.

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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, **OR**

f) Resectable colon cancer, **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 is 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, **OR**
4. Metastatic colorectal 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.

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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.

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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.

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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.

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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.

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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.

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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).

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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.

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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).

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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.

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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.

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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.

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Tumor Specific *KIT* Variant Analysis (Solid Tumor)

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

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

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

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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.

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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.

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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.

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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, **OR**

B. The member has a diagnosis of:

1. Local unresectable, recurrent, relapsed, refractory, metastatic, or advanced cancer, AND
2. The member has had progression of the cancer following prior treatment, AND
3. The member is considering treatment with an immune checkpoint inhibitor.

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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.

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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, progressive, or metastatic vaginal cancer, **OR**
13. Head and neck squamous cell carcinoma.

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

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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.

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TUMOR MUTATIONAL BURDEN (TMB) TESTING

Tumor Mutational Burden (TMB)

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

A. The member has a diagnosis of:

1. Local unresectable, recurrent, relapsed, refractory, metastatic, or advanced cancer, **AND**

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

C. The member is considering treatment with an immune checkpoint inhibitor, **AND**

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

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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**

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 Guardant Reveal and has one of the following:

a) Advanced colon cancer, **OR**

b) Colorectal 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) Advanced colon cancer, **OR**

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

c) Ovarian cancer, **OR**

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

e) Advanced breast cancer, **AND**

(1) The member has a diagnosis of disease recurrence or relapse, **OR**

f) Any solid tumor, **AND**

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

3. The member is being tested via Oncodetect and has the following:

a) Advanced colorectal cancer, **OR**

4. The member is being tested via RaDaR and has one of the following:

a) HPV-negative head and neck squamous cell carcinoma, **OR**

b) Advanced breast cancer, **OR**

5. The member is being tested via NavDx and has the following:

a) HPV-driven oropharyngeal cancer.

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

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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**.

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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.

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

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

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

4. Metastatic prostate cancer, **OR**

5. Stage III or IV cutaneous melanoma, **OR**
6. Metastatic colorectal cancer, **OR**
7. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
8. Persistent or recurrent cervical cancer, **OR**
9. Unresectable or metastatic biliary tract cancer, **OR**
10. Suspected or confirmed histiocytic neoplasm, **OR**
11. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine neoplasms, **OR**
12. Locoregional unresectable or metastatic large or small cell neuroendocrine neoplasms , **OR**
13. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm, **OR**
14. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**
15. Recurrent ovarian, fallopian tube or primary peritoneal cancer, **AND**
16. At least one of the following:
    a) The member is medically unfit for invasive tissue sampling (biopsy), **OR**
    b) Biopsy was performed, but material was insufficient for molecular analysis, **OR**
    c) Biopsy was performed, but molecular analysis was not able to be completely assessed on tissue due to availability of testing methodologies, **OR**
    d) Biopsy is not possible due to location of the tumor, **OR**

B. The member is being evaluated at diagnosis, progression, or recurrence of one of the following:

1. Recurrent or stage IV breast cancer, OR
2. Suspected or proven metastatic rectal cancer, **OR**
3. Suspected or proven metastatic colon cancer, **OR**
4. Locally advanced or metastatic lung adenocarcinoma, **OR**
5. Locally advanced or metastatic large cell lung carcinoma, **OR**
6. Locally advanced or metastatic squamous cell lung carcinoma, **OR**
7. Locally advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

C. The member has a diagnosis of metastatic prostate cancer, **AND**

1. The member is undergoing initial workup, **OR**

2. There is biochemical or radiologic evidence of recurrence or progression as demonstrated by either of the following:

a) Prostate specific antigen (PSA) is not undetectable, **OR**

b) There is radiographic progression.

II. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) performed simultaneously with solid tumor tissue testing is considered **medically necessary** when the member has one of the following diagnoses:

A. Lung adenocarcinoma, **OR**

B. Large cell lung carcinoma, **OR**

C. Squamous cell lung carcinoma, **OR**

1. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

III. 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.

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

I. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) 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.

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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.

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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.

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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.

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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.

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CIRCULATING TUMOR CELL (CTC) TESTS

Circulating Tumor Cell (CTC) Enumeration

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

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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.

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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.

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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.

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***NTRK* Fusion Analysis Panel for Solid Tumors**

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. Pediatric (diagnosed age 18 years or younger) diffuse high grade glioma.

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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.

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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.

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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.

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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 AND REFERENCES

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer (p. BINV-18).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline 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). Repeat testing can be considered by clinicians to guide future therapy decisions (p. COL-B 4 of 10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline 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 6 of 7). 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 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline 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 13).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Prostate Cancer (2.2025)

This guideline 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. This guideline also recommends that repeat tumor profiles can be considered at the time of progression of disease (p. PROS-C, 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Uterine Neoplasms (3.2025)

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Gastrointestinal Stromal Tumors (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GIST) 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

National Comprehensive Cancer Network (NCCN): Central Nervous System Cancers (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

National Comprehensive Cancer Network (NCCN): Rectal Cancer (2.2025)

This guideline states that repeat molecular testing can be considered by clinicians to guide future therapy decisions (p. REC-B 5 of 11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

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.

U.S. Food and Drug Administration. FoundationOne CDx: device labeling. PMA No. P170019. Published November 30, 2017. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf

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Targeted RNA Fusion Panels for Solid Tumors

National Comprehensive Cancer Network (NCCN): Central Nervous System Cancers (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Soft Tissue Sarcoma (1.2025)

This guideline states 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline recommends a gene fusion assay in the workup for Langerhans Cell Histiocytosis, (p. LCH-1A), Erdheim-Chester Disease, (p. ECD-1A) and Rosai-Dorfman Disease (p. RDD-1A). RNA-based molecular panels including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Gastrointestinal Stromal Tumors (1.2025)

This guideline states 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GIST) 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

American Society of Clinical Oncology (ASCO)

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).

Chakravarty D, Johnson A, Sklar J, et al. Somatic genomic testing in patients with metastatic or advanced cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. 2022;40(11):1231-1258. doi:10.1200/JCO.21.02767 Erratum in: J Clin Oncol. 2022;40(18):2068. doi:10.1200/JCO.22.01144

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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.

National Comprehensive Cancer Network. Biomarker Compendium. Accessed May 6, 2025. https://www.nccn.org/professionals/biomarkers/content/

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Colorectal Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends that all patients with suspected or proven metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF,* preferably as part of an NGS panel. This testing can be performed on the primary colorectal cancers and/or the metastasis (p. COL-2, COL-B, 4 of 10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

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Lung Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

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Cutaneous Melanoma Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

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Tumor Specific *BRAF* Variant Analysis

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

National Comprehensive Cancer Network (NCCN): Hairy Cell Leukemia (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hairy Cell Leukemia 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Central Nervous System Cancers (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma (p. COL-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Small Bowel Adenocarcinoma (3.2025)

This guideline recommends *BRAF* V600E testing for metastatic adenocarcinoma (p. SBA-5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

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Tumor Specific BRCA1/2 Variant Analysis

National Comprehensive Cancer Network (NCCN): Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Prostate Cancer (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

American Society of Clinical Oncology (ASCO)

ASCO published recommendations in an article called “Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer” (2020). 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).

Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245. doi:10.1200/JCO.19.02960

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Tumor Specific *EGFR* Variant Analysis

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

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Tumor Specific *ESR1* Variant Analysis

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends *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 15). Testing for *ESR1* mutations should occur at progression following the endocrine therapy (p. BINV-Q 6 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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Tumor Specific FOLR1 Protein Analysis

National Comprehensive Cancer Network (NCCN): Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

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Tumor Specific IDH1 and IDH2 Variant Analysis (Solid Tumor)

National Comprehensive Cancer Network (NCCN): Central Nervous System Cancers (1.2025)

This guideline recommends *IDH* mutation testing (*IDH1* and *IDH2*) in the work-up for all gliomas (p. BRAIN-E 2 of 9). Additionally, NCCN lists several preferred systemic treatment options for individuals with astrocytoma or oligodendroglioma who are *IDH*-mutant (p. GLIO-A 2 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

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Tumor Specific *KIT* Variant Analysis (Solid Tumor)

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline recommends testing for *KIT* gene mutations in patients with stage IV melanoma as this could impact treatment options (p. ME-9). Molecular testing is the preferred testing option, compared to *KIT* immunohistochemistry (IHC) (p. ME-C, 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Gastrointestinal Stromal Tumors (1.2025)

This guideline recommends *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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GIST) 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

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Tumor Specific *KRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline indicates 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Biliary Tract Cancers (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

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Tumor Specific *MGMT* Methylation Analysis

National Comprehensive Cancer Network (NCCN): Central Nervous System Cancers (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

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Tumor Specific *MLH1* Methylation Analysis

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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Tumor Specific Microsatellite Instability (MSI) Analysis

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends determination of tumor MMR or MSI in all individuals with newly diagnosed colorectal cancer (p. COL-B 4 of 10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Uterine Neoplasms (3.2025)

This guideline recommends MSI (among other studies) for patients undergoing initial evaluation for known or suspected uterine malignancy (p. ENDO-A 2 of 4, UTSARC-A 1 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends MSI testing for all newly diagnosed gastric cancers (p. GAST-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancer (3.2025)

This guideline recommends MSI by PCR or NGS for all patients with newly diagnosed esophageal and EGJ cancers (p. ESOPH-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline recommends MSI testing for patients with progressive, recurrent, or metastatic cervical carcinoma (p. CERV-A 1 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Testicular Cancer (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf

National Comprehensive Cancer Network (NCCN): Biliary Tract Cancers (2.2025)

This guideline recommends MSI testing for unresectable or metastatic gallbladder cancer or unresectable or metastatic intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma (p. BIL-B, 2 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends MSI testing for patients with recurrent unresectable or metastatic breast cancer considering a targeted therapy (p. BINV-Q, 7 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Small Bowel Adenocarcinoma (3.2025)

This guideline recommends universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma (p. SBA-B).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary (2.2025)

This guideline recommends MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology (p. OCC-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Vulvar Cancer (1.2025)

This guideline recommends consideration of MSI testing for recurrent, progressive or metastatic squamous cell carcinoma of the vulva (p. VULVA-A, 2 of 4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vulvar Cancer 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf

National Comprehensive Cancer Network (NCCN): Bone Cancer (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bone Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends consideration of MSI testing for recurrent or metastatic vaginal cancer (p. VAG-A 2 of 2, p. VAG-D 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025 https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

Food and Drug Administration (FDA)

The FDA has approved Keytruda (pembrolizumab) for use in **all** adult and pediatric patients with solid tumors that:

- Are unresectable or metastatic and
- Are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and
- Have progressed on prior treatment and
- Have no alternative treatment options (p. 1).

Merck & CO, Inc. KEYTRUDA (pembrolizumab). U.S. Food and Drug Administration. Website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf. Accessed 5/5/2025.

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Tumor Specific *NRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

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Tumor Specific PD-L1 Protein Analysis

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends PD-L1 testing during the workup for documented or suspected metastatic adenocarcinoma (p. GAST-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Head and Neck Cancers (4.2025)

This guideline recommends testing for PD-L1 status prior to treatment of salivary gland cancers (SALI-4), or for recurrent, unresectable, or metastatic non-oropharyngeal cancers (SYST-A 3 of 6), or for consideration of 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

National Comprehensive Cancer Network (NCCN): Bladder Cancer (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

National Comprehensive Cancer Network (NCCN): Vulvar Cancer (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vulvar Cancer 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends PD-L1 testing for individuals during the workup phase for documented or suspected metastatic esophageal and esophagogastric junction cancers (p. ESOPH-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline states recommendations for treatments for recurrent unresectable or stage IV triple negative breast cancer based on PD-L1 tumor status (p. BINV-Q 3 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends consideration of PD-L1 testing for recurrent, progressive, or metastatic vaginal cancer (p. VAG-5, VAG-6, VAG-A 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025 https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

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).

U.S. Food and Drug Administration. Premarket Approval (PMA) document: PD-L1 IHC 22C3 pharmDx (PMA No. P150013, Supplement S014). FDA website. Approved June 10, 2019. Accessed May 1, 2025. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150013S014

US Food and Drug Administration. Premarket Approval Document for PD-L1 IHC 22C3 pharmDx (PMA Number 150013/S020). FDA website. Approved November 13, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150013S020

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Tumor Specific *PIK3CA* Variant Analysis

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline 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.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Head and Neck Cancers (4.2025)

This guideline includes *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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

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Tumor Mutational Burden (TMB)

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends tumor mutational 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Biliary Tract Cancers (2.2025)

This guideline recommends tumor mutational burden testing for unresectable or metastatic gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma (p. BIL-B, 2 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends assessing for tumor mutational burden (TMB) during the workup of any stage colon cancer that is not mismatch-repair proficient (p. COL-2). The guideline states that patients with a high TMB have a better prognosis and respond well to immune checkpoint therapy, and describes direct *POLE/POLD1* gene mutation screening and direct measurement of tumor mutational burden as acceptable markers of the phenotype (p. COL-B 6 of 10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Rectal Cancer (2.2025)

This guideline recommends assessing tumor mutational burden (TMB) in non-mismatch repair proficient rectal cancer with or without suspected or proven distant metastases (p. REC-2, REC-3A), in recurrent metastatic rectal cancer (p. REC-11), and in pelvic anastomosis recurrence (p. REC-11A). The guideline also recommends TMB testing during the assessment for neoadjuvant definitive chemotherapy for locally unresectable/inoperable, T2-1 N1-2, or any N T3-4 rectal cancer (REC-14).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary Cancers (2.2025)

This guideline recommends tumor mutational burden testing for patients with suspected metastatic malignancy of uncertain pathology (p. OCC-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2025)

This guideline recommends tumor analysis, including tumor mutational burden (TMB), for recurrent, progressing, or treatment resistant ovarian/fallopian tube/primary peritoneal cancer (p. OV-B 1 of 3, OV-7, OV-8). TMB testing is recommended once during monitoring and follow up of low grade serous carcinoma if not previously done (LCOC-7) and in recurrent malignant germ cell/sex cord-stromal tumors (LCOC-A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Prostate Cancer (2.2025)

This guideline recommends somatic testing for tumor mutational burden for patients with metastatic castration-resistant prostate cancer (p. PROS-15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

National Comprehensive Cancer Network (NCCN): Testicular Cancer (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf

National Comprehensive Cancer Network (NCCN): Uterine Neoplasms (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Bone Cancer (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bone Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline 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, 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Head and Neck Cancers (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends consideration of tumor mutational burden for patients with locally recurrent/persistent, radioactive iodine refractory, 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

ational Comprehensive Cancer Network (NCCN): Vulvar Cancer (1.2025)

This guideline recommends consideration of tumor mutational burden (TMB) testing in the pathologic assessment for squamous cell carcinoma of the vulva (p. VULVA-A, 2 of 4) or when considering second-line or subsequent therapy in advanced, recurrent, or metastatic squamous cell carcinoma and adenocarcinoma of the vulva (p. VULVA-E 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vulvar Cancer 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf

National Comprehensive Cancer Network (NCCN): Small Bowel Adenocarcinoma (3.2025)

This guideline recommends consideration of tumor mutational burden testing for metastatic adenocarcinoma (p. SBA-5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025 https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

Food and Drug Administration (FDA)

The FDA has approved Keytruda (pembrolizumab) for use in **all** adult and pediatric patients with non-central nervous system solid tumors that:

- Are unresectable or metastatic and
- Have a high (≥10 mutations/megabase) tumor mutational burden and
- Have progressed on prior treatment and
- Have no alternative treatment options (p. 1).

Merck & CO, Inc. KEYTRUDA (pembrolizumab). U.S. Food and Drug Administration. Website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf. Accessed 5/5/2025.

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

Centers for Medicare and Medicaid Services (CMS)

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:

- 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.
- The MRD test [unless it is a Food and Drug Administration (FDA) approved and established standard-of-care single-gene polymerase chain reaction (PCR)] satisfactorily completes a technical assessment (TA) that will evaluate and confirm that the analytical validity, clinical validity, and clinical utility criteria set in this policy are met to establish the test as Reasonable and Necessary"

"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."

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Minimal Residual Disease Testing for Cancer (L38779). Effective Date: 12/26/2021. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38779

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.

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Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing

Concert Note

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.

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

Centers for Medicare and Medicaid Services (CMS)

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.”

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Minimal Residual Disease Testing for Cancer (L38779). Effective Date: 12/26/2021. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38779

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.

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

National Comprehensive Cancer Network (NCCN): Prostate Cancer (2.2025)

This guideline recommends evaluating prostate tumors 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 feasible, but should be collected when there is radiographic or biochemical progression (ie elevated PSA) to reduce the risk of false negatives. In patients with undetectable PSA levels, the NCCN recommends against ctDNA collection (PROS-C, 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced gastric cancer who may be unable to safely undergo a traditional biopsy (p. GAST-B 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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-6A, PANC-9, PANC-10, PANC-11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends 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 or when insufficient tumor tissue is available (p. ESOPH-B 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends broad molecular profiling for detection of mutations in *RAS*, *BRAF* and other genes along with *HER2* amplifications and MSI during the initial workup or at recurrence in patients with suspected or proven metastatic adenocarcinoma (COL-2, COL-9). Testing may be done via blood- or tissue-based NGS panels (COL-B 4 of 10). NCCN recommends consideration of repeat testing after targeted therapy to guide future treatment decisions (p. COL-B, 4 of 10). The NCCN does not recommend molecular profiling via ctDNA for surveillance or de-escalation of care (COL-8, COL-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline supports 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 recommends tissue testing if testing via ctDNA is negative due to the risk of false negatives (ME-C 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends 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. MS-5, AMP-3, AMP-6, AMP-7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline 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-10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Biliary Tract Cancers (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline mentions molecular testing in the workup for histiocytosis and states that if biopsy is not possible due to location or risk factors, mutational analysis of peripheral blood is an option (p. LCH-1A, ECD-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline 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, pheochromocytoma/paraganglioma, and atypical carcinoid neoplasms when systemic therapy is being considered (NET-6, NET-11, NET-12, WDG3-1, PHEO-1). 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary (2.2025)

This guideline recommends consideration of molecular profiling of tumor tissue after an initial determination of histology has been made. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. OCC-1A, OCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends the use of comprehensive somatic profiling for patients with stage IV or recurrent invasive breast cancer to identify candidates for additional targeted therapies (BINV-18, BINV-Q 6 of 15). Biomarker testing should be done on at least the first recurrence, and either tissue or plasma based assays can be used, and testing of an alternate specimen can be considered if one is negative for actionable biomarkers (p. BINV-18).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

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***EGFR* Variant Analysis via ctDNA**

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

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).

Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP

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BRAF Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline recommends *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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

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KRAS Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

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PIK3CA Variant Analysis via ctDNA

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends *PIK3CA* mutation testing for patients with hormone receptor positive/HER2 negative recurrent unresectable or stage IV breast cancer to identify candidates for treatment with alpelisib or capivarsertib, plus fulvestrant, as a preferred second or subsequent line of therapy. Testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If the liquid biopsy is negative, tumor tissue testing is recommended (p. BINV-Q, 6 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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Circulating Tumor Cell (CTC) Enumeration

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline mentions 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-76).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Centers for Medicare and Medicaid Services (CMS)

In the CMS local coverage determination (LCD) entitled "MolDX: Phenotypic 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".

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Phenotypic Biomarker Detection in Circulating Tumor Cells (L38566). Effective Date: 06/02/2022. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38566

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

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends *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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Histiocytic Neoplasms (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Pediatric Central Nervous System Cancers (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Central Nervous System 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf

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Bladder Cancer Diagnostic and Recurrence FISH Tests

Centers for Medicare and Medicaid Services (CMS)

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."

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. Lab: Bladder/Urothelial Tumor Markers (L33420). Effective Date: 03/04/2021. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33420&ver=41

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

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Head and Neck Cancers (4.2025)

This guideline recommends HER2/*ERBB2* testing prior to treatment for individuals diagnosed with recurrent, unresectable, or metastatic salivary gland tumors (p. SALI-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends HER2/*ERBB2* testing be performed on all patients with newly diagnosed primary or metastatic breast cancer (p. BINV-A 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline recommends HER2 testing for recurrent, advanced or metastatic cervical carcinoma (p. CERV-A 1 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Uterine Neoplasms (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer/Fallopian Tube Cancer/Peritoneal Cancer (3.2025)

This guideline recommends HER2 testing by IHC for recurrent disease after primary treatment (p. OV-6).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends consideration of HER2 testing by IHC or FISH for recurrent or metastatic vaginal cancer (p. VAG-D 1 of 2VAG-A 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

National Comprehensive Cancer Network (NCCN): Bladder Cancer (1.2025)

This guideline recommends consideration of IHC for HER2 overexpression for stage IIIB or higher muscle invasive bladder cancer (p. BL-8 through BL-10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

National Comprehensive Cancer Network (NCCN): Small Bowel Adenocarcinoma (3.2025)

This guideline recommends testing for HER2 amplifications for patients with metastatic disease (p. SBA-5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf

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NTRK Fusion Analysis Panel for Solid Tumors

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends 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 12).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Occult Primary (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline recommends *NTRK* fusion analysis for patients with cervical sarcoma (p. CERV-A 1 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Vulvar Cancer (1.2025)

This guideline recommends consideration of *NTRK* fusion analysis for recurrent, progressive, or metastatic squamous cell carcinoma of the vulva (p. VULVA-A 2 of 4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vulvar Cancer 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf

National Comprehensive Cancer Network (NCCN): Uterine Neoplasms (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends *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 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Soft Tissue Sarcoma (1.2025)

This guideline recommends larotrectinib, entrectinib or repotrectinib for patients with advanced or metastatic disease and *NTRK* gene fusion-positive tumors (p. SARC-G 1 of 13).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline 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 6 of 12).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Head and Neck Cancers (4.2025)

This guideline recommends use of NGS profiling and other appropriate biomarker testing to evaluate *NTRK* prior to treatment for metastatic salivary gland tumors (p. SALI-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

National Comprehensive Cancer Network (NCCN): Hepatocellular Carcinoma (1.2025)

This guideline states that larotrectinib, entrectinib, and repotrectinib are options for treatment in patients with *NTRK* gene fusion positive tumors (p. HCC-I, 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf

National Comprehensive Cancer Network (NCCN): Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN): Small Bowel Adenocarcinoma (3.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf

National Comprehensive Cancer Network (NCCN): Pediatric Central Nervous System Cancers (2.2025)

This guideline states 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Central Nervous System 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends consideration of *NTRK* fusion testing for recurrent or metastatic vaginal cancer (p. VAG-5, VAG-6, VAG-A 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025 https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

National Comprehensive Cancer Network (NCCN): Gastrointestinal Stromal Tumors (1.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GIST) 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

Food and Drug Administration (FDA)

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."

U.S Food and Drug Administration. Labeling for Augtyro (repotrectinib) (NDA No. 218213). FDA website. Approved November 15, 2023. Updated June 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218213s001lbl.pdf

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Tumor Specific *RET* Gene Rearrangement Tests (FISH)

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Cervical Cancer (4.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline lists *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, 7 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN): Colon Cancer (4.2025)

This guideline recommends broad molecular profiling including *RET* fusion detection as part of the workup for suspected or proven metastatic adenocarcinoma (p. COL-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Esophageal and Esophagogastric Junction Cancers (3.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

National Comprehensive Cancer Network (NCCN): Gastric Cancer (2.2025)

This guideline recommends consideration of *RET* gene fusion testing for patients with locally advanced, recurrent or metastatic gastric cancer (p. GAST-B, 5 of 6).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

National Comprehensive Cancer Network (NCCN): Vaginal Cancer (5.2025)

This guideline recommends consideration of *RET* fusion testing for recurrent or metastatic vaginal cancer (p. VAG-D 1 of 2 and VAG-A 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

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Tumor Specific *ROS1* Gene Rearrangement

National Comprehensive Cancer Network (NCCN): Non-Small Cell Lung Cancer (7.2025)

This guideline recommends *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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 7.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

National Comprehensive Cancer Network (NCCN): Pancreatic Adenocarcinoma (2.2025)

This guideline 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN): Pediatric Central Nervous System Cancers (2.2025)

This guideline states 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).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Central Nervous System 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf

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Cancer Exome and Genome Sequencing

Concert Evidence Review for Coverage Determination (Published 06/01/2025)

This review focused on a search for evidence-based guidelines and peer-reviewed, published evidence of the clinical utility of cancer exome and genome sequencing from 05/21/2024 - 05/21/2025. A total of 63 abstracts were identified and 13 references were fully reviewed, none of which met the inclusion criteria.

Based on this review, there were no new guidelines and no peer-reviewed literature identified to include in the evidence review.

There is INSUFFICIENT EVIDENCE in published guidelines and peer-reviewed literature to definitively demonstrate improved health outcomes from the use of cancer exome and genome sequencing, as compared to the current standard of care. At this time, the available evidence does not support health plan coverage of these tests compared to other guideline-supported testing methodologies.

Concert Evidence Review for Coverage Determination for Cancer Exome And Genome Sequencing. Published 06/01/2025.

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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).

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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.

Medica Central Coverage Policy

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