Revision log

CONCERT GENETICS ONCOLOGY: MOLECULAR ANALYSIS OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

The molecular analysis of solid tumors and hematologic malignancies aims to identify somatic oncogenic mutations in cancer. These mutations, often called “driver” mutations, are becoming increasingly useful for targeted therapy selection, and may give insight into prognosis and treatment response in a subset of cancers. In addition, molecular analysis of solid tumors and hematologic malignancies, in particular, can also aid in making a diagnosis of a specific type of malignancy. For solid tumors, molecular analysis can be performed via direct testing of the tumor (which is addressed in this policy) or via circulating tumor DNA or circulating tumor cells (CTCs) (see Other Related Policies). For hematologic malignancies, molecular analysis can be performed on blood samples or bone marrow biopsy samples.

For individuals with advanced cancer, somatic genomic profiling offers the potential to evaluate a large number of genetic markers in the cancer simultaneously in order to provide potential treatment options beyond the current standard of care.

While the primary goal of the molecular analysis of solid tumors and hematologic malignancies is to identify biomarkers that diagnose or to 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. Current tumor testing strategies include tumor-only testing, tumor-normal paired testing with germline variant subtraction, and tumor-normal paired testing with explicit analysis of a group of genes associated with germline cancer predisposition. This is an

evolving area and clear guidelines around the optimal approach for identification and reporting of the presumed germline pathogenic variants (PGPVs) are emerging.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies				
Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests	FoundationOne CDx (Foundation Medicine)	0037U	C00-D49, Z85	1, 2, 4, 5, 7, 25, 26, 31
	MSK-IMPACT (Memorial Sloan Kettering Medical Center)	0048U		
	Oncomap ExTra (Exact Sciences Laboratories, LLC)	0329U		
	OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs)	81445, 81455		
	Tempus xT (Tempus)			
	Precise Tumor (Myriad)			
	Guardant360 TissueNext (Guardant)	0334U		
	PGDx elio tissue complete (Personal Genome Diagnostics, Inc)	0250U		

	OmniSeq INSIGHT, Solid Tumor NGS Panel (DNA and RNA) (Labcorp Oncology)	81455		
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)			
	Solid Tumor Expanded Panel (Quest Diagnostics)	0379U		
Targeted RNA Fusion Panel Tests	Targeted Solid Tumor NGS Fusion Panel (NeoGenomics)	81449, 81451	C91, C34, C71, C49, C96	1, 8, 17, 20, 35, 38, 39, 40
Broad RNA Fusion Panel Tests	Tempus xR Whole Transcriptome RNA Sequencing (Tempus)	81456	C00-C80	
Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81455	C91, C92, D46.9	6, 10, 12, 15, 17
	Tempus xT Hematologic Malignancy (Tempus)			
	NeoTYPE Myeloid Disorders Profile (NeoGenomics Laboratories)	81450		
	OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies (Mayo Clinic Laboratories)			
	Onkosight Advanced NGS Myeloid Panel (BioReference Laboratories)			
Colorectal Cancer Focused Molecular Profiling Panels	Praxis Extended RAS Panel (Illumina)	0111U	C18-C20	2
	Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)	81445		
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test (NeoGenomics Laboratories)	0022U	C34	1
	OnkoSight Advanced Comprehensive Lung (BioReference Laboratories)	81445		
Cutaneous Melanoma Focused Molecular Profiling Panels	MelanomaSeqPlus (Quest Diagnostics)	81445	C43, D03	9
	OnkoSight Melanoma Panel (BioReference Laboratories)			

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML Gene Panel Assay (LabPMM, Invivoscribe Technologies)	0050U	C92, D47	10
	NeoTYPE AML Prognostic Profile (NeoGenomics)	81450		
	LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)			
Myeloproliferative Neoplasms (MPNs) Panel Tests	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories)	81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339	D47	12
	OnkoSight Advanced NGS JAK2, MPL, CALR Panel (BioReference Laboratories)			
Single Gene Testing of Solid Tumors and Hematologic Malignancies				
Tumor Specific *BCR/ABL1* Kinase Domain Analysis	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170	C91, C92	15, 16, 17
	Onkosight NGS ABL1 Sequencing (BioReference Laboratories)			
Tumor Specific *BCR/ABL1* Quantitation and Breakpoint Analysis	BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics)	81206, 81207	C83, C85, C91, C92, D45, D47	10, 12, 15, 16,17,18
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (Labcorp)			
	BCR/ABL1 (T(9;22)) RNA Quantitative with Interpretation (University of Iowa)	0016U		
	MRDx BCR-ABL Test (MolecularMD)	0040U		
Tumor Specific *BRAF* Variant Analysis	BRAF Mutation Analysis (NeoGenomics)	81210	C18-C21, C34, C43, C71, C73, C91.4	1, 2, 9, 13, 19,20
Tumor Specific *BRCA1/2* Variant Analysis	BRCA1/2 Mutation Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81162, 81163, 81164, 81165, 81166, 81167, 81216	C56, C61	5, 7, 22, 25
	BRCA1/2 Mutation Analysis for Tumors (NeoGenomics Laboratories)			

Tumor Specific *CALR* Variant Analysis	Calreticulin (CALR) Mutation Analysis (Quest Diagnostics)	81219	C94 D47.1	12
Tumor Specific *CEBPA* Variant Analysis	CEBPA Mutation Analysis (Labcorp)	81218	C92	10
Tumor Specific *EGFR* Variant Analysis	EGFR Mutation Analysis (NeoGenomics Laboratories)	81235	C34	1
Tumor Specific *ESR1* Variant Analysis	ESR1 Mutations Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81479	C50	4
Tumor Specific *FLT3* Variant Analysis	FLT3 ITD and TKD Mutation (PCR) (PathGroup)	81245, 81246	C92	10
	LeukoStrat CDx FLT3 Mutation Assay (Versiti)	0023U		
	FLT3 ITD MRD by NGS (LABPMM, Invivoscribe Technologies)	0046U		
Tumor Specific *IDH1* and *IDH2* Variant Analysis	IDH1/IDH2 Mutation Analysis (NeoGenomics)	81120, 81121	C71, C92, D49.6	10, 20
Tumor Specific *IGHV* Somatic Hypermutation Analysis	IgVH Mutation Analysis (NeoGenomics)	81261, 81262, 81263	C83, C91, D47.Z1	18, 28, 36
Tumor Specific *JAK2* Variant Analysis	JAK2 Exons 12 to 15 Sequencing (Mayo Clinic Laboratories)	0027U	C91, C92, C94, D45, D47.1, D47.3, D75.81	6, 12, 16
	JAK2 Mutation (University of Iowa)	0017U		
	JAK2 V617F Mutation Analysis (Quest Diagnostics)	81270		
Tumor Specific *KIT* Variant Analysis	KIT Mutation Analysis (ProPath)	81272, 81273	C43, C49.A, C92, D47.1, D47.02	8, 9, 10, 11
	KIT (D816V) Digital PCR (Labcorp)			
Tumor Specific *KRAS* Variant Analysis	KRAS Mutation Analysis (NeoGenomics)	81275, 81276	C18-21, C34	1, 2, 24
Tumor Specific *MGMT* Methylation Analysis	MGMT Promoter Methylation -Tumor (Ohio State University Molecular Pathology Laboratory)	81287	C71	20

Tumor Specific *MLH1* Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics)	81288	C18-C21, C54.1	3, 23
Tumor Specific *MPL* Variant Analysis	MPL Mutation Analysis (Quest Diagnostics)	81338, 81339	D45, D47.1, D47.3, D75.81	12
Tumor Specific Microsatellite Instability (MSI) Analysis	Microsatellite Instability (MSI) by PCR (NeoGenomics)	81301	C15-C23, C50, C53, C54.1, C62, C80	2, 4, 7,14, 26, 27, 29, 30, 31, 32, 34
	Microsatellite Instability (MSI) (Quest Diagnostics)			
Tumor Specific *NPM1* Variant Analysis	NPM1 MRD by NGS (LabPMM, Invivoscribe Technologies)	0049U	C92	10
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)	81310		
Tumor Specific *NRAS* Variant Analysis	NRAS Mutation Analysis (NeoGenomics)	81311	C18-C21	2, 24
Tumor Specific *PIK3CA* Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309	C50, C55	4, 14
	PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp)	0155U, 0177U		
Tumor Specific *TP53* Variant Analysis	TP53 Mutation Analysis (NeoGenomics)	81352	C92, R71, R79	10, 18, 28
Measurable (Minimal) Residual Disease (MRD) Analysis				
Hematologic Minimal Residual Disease (MRD) Analysis	MyMRD NGS Panel,(LABPMM, Invivoscribe Technologies)	0171U	C91, R71, R79	17, 28, 33
	ClonoSEQ (Adaptive Biotechnologies)	0364U		
Solid Tumor Minimal Residual Disease (MRD) Analysis	Signatera - Residual Disease Test (MRD) - (Natera)	0340U	C00-D49, Z85	2, 4
	PCM Tissue Profiling and MRD Baseline Assay (Invitae)	0306U		
	PCM MRD Monitoring (Invitae)	0307U		
	Guardant360 Response (Guardant Health, Inc)	0422U		

	RaDaR (NeoGenomics)	81479		
	Colvera (Clinical Genomics Pathology)	0229U		
Tumor Mutational Burden (TMB)				
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479	C00-D49, Z85	4, 5, 7, 14, 25, 29, 30, 31, 32
Red Blood Cell Genotyping in Multiple Myeloma				
Red Blood Cell Genotyping in Multiple Myeloma	PreciseType HEA (Immucor)	0001U	C90.0, R71, R79	37
	Navigator ABO Sequencing (Grifols Immunohematology Center)	0180U		
	Navigator ABO Blood Group NGS (Grifols Immunohematology Center)	0221U		
Cancer Exome and Genome Sequencing				
Cancer Exome/Genome Sequencing	Praxis Somatic Whole Genome Sequencing (Praxis Genomics)	0297U	C00-D49, Z85	35
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	81415, 81416, 81425, 81426		
	Tempus xE (Tempus)			
	EXaCT-1 Whole Exome Testing (Weill Cornell Medicine)	0036U		
Genetic Testing to Confirm the Identity of Laboratory Specimens				
Genetic Testing to Confirm the Identity of Laboratory Specimens	know error DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC)	81265, 81266, 81479	C00.0-D49	35
	ToxProtect (Genotox Laboratories LTD)	0007U		

OTHER RELATED POLICIES

This policy document provides criteria for molecular analysis of solid tumors and hematologic malignancies. Please refer to:

- ***Oncology: Cytogenetic Testing*** for criteria related to tumor testing with IHC, FISH, etc. (e.g., ALK, BCR/ABL FISH analysis, ERBB2 [HER2] IHC analysis, NTRK fusion analysis, ROS1 analysis)
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance.
- ***Oncology: Algorithmic Testing*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Genetic Testing: Whole Genome and Whole Exome Sequencing for the Diagnosis of Genetic Disorders*** for criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to tumor and hematologic malignancy testing that is not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests

I. Tumor-type agnostic solid tumor molecular profiling panel tests (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U) are considered **medically necessary** when:

   A. The member/enrollee has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **AND**

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

II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0334U, 0379U) is considered **medically necessary** when:

   A. The member/enrollee has progression of any of the following:

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

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

      3. Metastatic prostate cancer

III. Tumor-type agnostic solid tumor molecular profiling panel tests (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U) 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 Panel Tests

I. RNA specific fusion panel tests with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449, 81451) are considered **medically necessary** when:

   A. The member/enrollee is undergoing workup for adult or pediatric acute lymphoblastic leukemia (ALL), **OR**

B. The member/enrollee has a diagnosis of glioma, **OR**

C. The member/enrollee is undergoing workup for histiocytosis, **OR**

D. The member/enrollee is undergoing workup for a sarcoma, **OR**

E. The member/enrollee has a gastrointestinal stromal tumor, **AND**

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

F. The member/enrollee has non-small cell lung cancer, **AND**

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

G. The member/enrollee 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. RNA specific fusion panel tests (81449, 81451) are considered **investigational** for all other indications.

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Broad RNA Fusion Panel Tests

I. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (81456) are considered **investigational**.

Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

I. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **medically necessary** when:

A. The member/enrollee has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML), **OR**

B. The member/enrollee has newly diagnosed acute lymphoblastic leukemia (ALL), **OR**

C. The member/enrollee has newly diagnosed myelodysplastic syndrome (MDS), **OR**

D. The member/enrollee has suspected myelodysplastic syndrome (MDS) and other causes of cytopenia(s) have been ruled out, **OR**

E. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **AND**

1. This is the member/enrollee's initial genetic evaluation for suspected MPN, **OR**

2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative, **OR**

F. The member/enrollee has a diagnosis of chronic myelogenous leukemia (CML), **AND**

1. There has been progression to accelerated or blast phase, **OR**

2. Results of *BCR-ABL1* kinase domain mutation analysis were negative.

II. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **medically necessary** when:

A. The member/enrollee has myelodysplastic syndrome (MDS), **AND**

1. The member/enrollee has relapsed after allo-HCT [hematopoietic cell transplant], **OR**

B. The member/enrollee has acute lymphoblastic leukemia (ALL), **AND**

1. The member/enrollee is showing evidence of symptomatic relapse after maintenance therapy, **OR**

C. The member/enrollee has acute myeloid leukemia (AML), **AND**

1. The member/enrollee has relapsed or refractory disease or progression on treatment.

III. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered investigational for all other indications.

Note: If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies.

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Colorectal Cancer Focused Molecular Profiling Panels

I. Colorectal cancer focused molecular profiling panels (0111U, 81445) in solid tumors are considered **medically necessary** when:

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

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

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

D. One of the following:

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

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

II. Colorectal cancer-focused molecular profiling panels (0111U, 81445) 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 (0022U, 81445) are considered **medically necessary** when:

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

      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/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy).

II. Repeat lung cancer-focused molecular profiling panels (0022U, 81445) is medically necessary when the member/enrollee has progression on targeted therapy for non-small cell lung cancer.

III. Lung cancer-focused molecular profiling panels (0022U, 81445) 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 (81445) are considered **medically necessary** when:

   A. The member/enrollee has a new diagnosis of stage IV melanoma or has recurrent melanoma, **AND**

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

C. One of the following:

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

2. The member/enrollee *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 (81445) are considered **investigational** for all other indications.

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

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Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

I. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **medically** necessary when:

A. The member/enrollee has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).

II. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) is considered **investigational** for all other indications.

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

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Myeloproliferative Neoplasms (MPNs) Panel Tests

I. Myeloproliferative neoplasm (MPN) molecular profiling panel tests (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **medically necessary** when:

A. The member/enrollee is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **AND**

B. The panel does not include genes other than *JAK2*, *CALR*, *MPL*, and *BCR/ABL1*.

II. Myeloproliferative neoplasm (MPN) molecular profiling panel tests (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **investigational** for all other indications.

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SINGLE-GENE TESTING OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

Tumor Specific *BCR/ABL1* Kinase Domain Analysis

I. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of chronic myeloid leukemia (CML) or Ph-like acute lymphocytic leukemia (ALL), **AND**

B. Any of the following:

1. Initial response to TKI therapy is inadequate, **OR**
2. Loss of response to TKI therapy, **OR**
3. Disease progression to the accelerated or blast phase, **OR**
4. Relapsed/refractory disease.

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Tumor Specific *BCR/ABL1* Quantitation and Breakpoint Analysis

I. Tumor specific *BCR/ABL1* quantitation and breakpoint analysis (0016U, 0040U, 81206, 81207) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**

B. The member/enrollee is undergoing workup for or to monitor disease progression (i.e., for minimal residual disease (MRD) monitoring) of:

1. Acute lymphoblastic leukemia (ALL), **OR**
2. Acute myeloid leukemia (AML), **OR**
3. Chronic myelogenous leukemia (CML), **OR**
4. B-cell lymphoma.

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Tumor Specific *BRAF* Variant Analysis

I. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee 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 locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma, **OR**
6. Low-grade glioma or pilocytic astrocytoma, **OR**

B. The member/enrollee is being evaluated for:

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

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Tumor Specific *BRCA1/2* Variant Analysis

I. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of:

1. Ovarian, fallopian tube and/or primary peritoneal cancer, **OR**
2. Metastatic prostate cancer, **OR**
3. Locally advanced/metastatic pancreatic cancer

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Tumor Specific *CALR* Variant Analysis

I. Tumor specific *CALR* variant analysis (81219) is considered **medically necessary** when:

A. The member/enrollee displays clinical symptoms of a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.

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Tumor Specific *CEBPA* Variant Analysis

I. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee has cytogenetically normal acute myeloid leukemia (AML).

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Tumor Specific *EGFR* Variant Analysis

I. Tumor specific *EGFR* variant analysis (81235) in solid tumors is considered **medically necessary** when:

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

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 (81479) in solid tumors is considered **medically necessary** when:

A. The member/enrollee is a postmenopausal female or adult male with the following:

1. ER-positive and HER2-negative breast cancer, **AND**
2. 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 *FLT3* Variant Analysis

I. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee has suspected or confirmed acute myeloid leukemia (AML), **OR**

B. The member/enrollee has a diagnosis of acute lymphocytic leukemia (ALL), **OR**

C. The member/enrollee has a diagnosis of myelodysplastic syndrome (MDS).

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Tumor Specific *IDH1* and *IDH2* Variant Analysis

I. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of a glioma, **OR**

B. The member/enrollee has a diagnosis of acute myeloid leukemia (AML).

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Tumor Specific *IGHV* Somatic Hypermutation Analysis

I. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of:

1. Chronic lymphocytic leukemia (CLL), **OR**
2. Small lymphocytic leukemia (SLL), **OR**
3. Primary cutaneous B-cell lymphoma, **OR**
4. Mantle cell lymphoma, **OR**
5. Post-transplant lymphoproliferative disorder.

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Tumor Specific *JAK2* Variant Analysis

I. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**

B. The member/enrollee has acute lymphoblastic leukemia (ALL), **OR**

C. The member/enrollee is suspected to have a myelodysplastic syndrome (MDS).

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Tumor Specific *KIT* Variant Analysis

I. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee is suspected to have, or is being evaluated for systemic mastocytosis, **OR**

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

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

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

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Tumor Specific *KRAS* Variant Analysis

I. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors is considered **medically necessary** when:

A. The member/enrollee meets one of the following:

1. The member/enrollee has suspected or proven metastatic colorectal cancer, **OR**

2. The member/enrollee is undergoing workup for metastasis of non-small cell lung cancer.

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Tumor Specific *MGMT* Methylation Analysis

I. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a high grade glioma (stage III or IV), including one of the following:

1. Anaplastic oligodendroglioma, **OR**
2. Anaplastic astrocytoma, **OR**
3. Anaplastic glioma, **OR**
4. Glioblastoma.

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Tumor Specific *MLH1* Methylation Analysis

I. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND**

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

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Tumor Specific *MPL* Variant Analysis

I. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee displays clinical symptoms of a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.

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Tumor Specific Microsatellite Instability (MSI) Analysis

I. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of:

1. Colorectal cancer, **OR**
2. Endometrial cancer, **OR**
3. Gastric cancer, **OR**
4. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer, **OR**
5. Recurrent, progressive or metastatic cervical cancer, **OR**
6. Testicular cancer (nonseminoma) 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. Unresectable or metastatic breast cancer, **OR**
10. Small bowel adenocarcinoma, **OR**
11. Metastatic pancreatic cancer, **OR**
12. Metastatic occult primary.

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Tumor Specific *NPM1* Variant Analysis

I. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies is considered **medically necessary** when:

A. The member/enrollee has cytogenetically normal acute myeloid leukemia (AML).

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Tumor Specific *NRAS* Variant Analysis

I. Tumor specific *NRAS* variant analysis (81311) in solid tumors is considered **medically necessary** when:

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

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Tumor Specific *PIK3CA* Variant Analysis

I. Tumor specific *PIK3CA* variant analysis (81309, 0155U, 0177U) in solid tumors is considered **medically necessary** when:

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

B. The member/enrollee has a diagnosis of uterine rhabdomyosarcoma.

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Tumor Specific *TP53* Variant Analysis

I. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood is considered **medically necessary** when:

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

B. The member/enrollee has a diagnosis of chronic lymphocytic leukemia (CLL), **OR**

C. The member/enrollee has a diagnosis of small lymphocytic leukemia (SLL), **OR**

D. The member/enrollee is undergoing diagnostic workup for mantle cell lymphoma (MCL).

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MEASURABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS

Hematologic Minimal Residual Disease (MRD) Testing

I. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood is **medically necessary** when:

   A. The member/enrollee has a diagnosis of:

      1. Acute Lymphocytic Leukemia (ALL), **OR**
      2. Multiple Myeloma, **OR**
      3. Chronic Lymphocytic Leukemia (CLL).

Solid Tumor Minimal Residual Disease (MRD) Testing

I. Measurable (minimal) residual disease (MRD) analysis (0229U, 0340U, 0306U, 0307U, 0422U, 81479) in solid tumor tissue is considered **investigational.**

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TUMOR MUTATIONAL BURDEN (TMB)

I. Tumor mutational burden (TMB) testing (81479) is considered **medically necessary** when:

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

      1. Recurrent or metastatic breast cancer, **OR**
      2. Recurrent, progressive or metastatic cervical cancer, **OR**

3. Unresectable or metastatic gallbladder cancer, **OR**
4. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma, **OR**
5. Suspected metastatic malignant occult primary tumor, **OR**
6. Recurrent ovarian/fallopian tube/primary peritoneal cancer, **OR**
7. Metastatic or advanced pancreatic adenocarcinoma, **OR**
8. Metastatic castration-resistant prostate cancer, **OR**
9. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy, **OR**
10. Endometrial carcinoma or uterine sarcoma.

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RED BLOOD CELL GENOTYPING IN MULTIPLE MYELOMA

I. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma is considered **medically necessary** when:

   A. The member/enrollee has a diagnosis of multiple myeloma, **AND**

   B. The member/enrollee is currently being treated or will be treated with Daratumumab (DARA).

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CANCER EXOME AND GENOME SEQUENCING

I. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0036U, 0297U, 81415, 81416, 81425, 81426) is considered **investigational**.

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GENETIC TESTING TO CONFIRM THE IDENTITY OF LABORATORY SPECIMENS

I. Genetic testing to confirm the identity of laboratory specimens (e.g., known error, ToxProtect) (0007U, 81265, 81266, 81479), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance.

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NOTES AND DEFINITIONS

1. **Tumor mutation burden** testing is 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.

2. **Advanced cancer** is 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.

3. **Myeloproliferative Neoplasms** are rare overlapping blood diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets.

   There are seven subcategories of myeloproliferative neoplasms:

   - Chronic myeloid leukemia (CML)
   - Polycythemia vera (PV)
   - Primary myelofibrosis (PMF)
   - Essential thrombocytopenia (ET)
   - Chronic neutrophilic leukemia
   - Chronic eosinophilic leukemia
   - Chronic eosinophilic leukemia-not otherwise specified
   - MPN, unclassifiable (MPN-U)

4. **Myelodysplastic Syndromes (MDS)** are a group of disorders characterized by abnormalities of the bone marrow, leading to low numbers of one or more types of blood cells. The WHO system recognizes 6 main types of MDS:

   - MDS with multilineage dysplasia (MDS-MLD)

- MDS with single lineage dysplasia (MDS-SLD)
- MDS with ring sideroblasts (MDS-RS)
- MDS with excess blasts (MDS-EB)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

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CLINICAL CONSIDERATIONS

Clinical decision making should not be made based on variants of uncertain significance.

NCCN and ASCO recommend that all individuals diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer have germline and somatic tumor testing (if not previously performed) for *BRCA1* and *BRCA2* mutations.

The genetic testing of tumors and hematologic malignancies (somatic mutation profiling) may reveal incidental germline findings or suspicion of a clinically significant germline mutation. Providers should communicate the potential for these incidental findings with their patients prior to somatic mutation profiling.

ACMG (2020) recognized that tumor testing is an emerging area and that the identification of presumed germline pathogenic variants (PGPVs) have profound health and reproductive implications for the individual with cancer as well as their family members. Thus, individuals undergoing tumor testing should be informed prior to testing that a germline variant may be uncovered. PGPVs should be carefully evaluated, confirmed, and reported when tumor testing is performed. Currently, there is a lack of evidence for best practices to report PGPVs to patients who want them.

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BACKGROUND AND RATIONALE

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (4.2023) recommend comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer. (p. BINV-18)

The NCCN guideline on Occult Primary (3.2023) recommends MSI and MMR testing as part of the initial work up for patients with cancer of unknown primary. The guideline further recommends consideration of NGS to identify actionable genomic aberrations after a histological determination of the tumor has been made. (p. OCC-1)

The NCCN guideline on Non-Small Cell Lung Cancer (3.2023) recommends molecular testing for advanced or metastatic disease, including *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3*, *MET*ex14 skipping, *RET, PD-L1*. They also recommend broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available. (p. NSCL-18). The guidelines also state that repeat somatic genetic testing can be helpful to aid in deciding next therapeutic steps when a patient's tumor shows evidence of progression on first-line therapy. (p. NSCL-H 6 of 7)

The NCCN guideline for Colon Cancer (2.2023) recommends all patients with metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. Testing can be performed on the primary tumor and/or metastases (p. COL-B 4 of 8)

The NCCN guideline for Gastric Cancer (1.2023) recommends that patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering an FDA approved therapy undergo comprehensive genomic profiling via a validated NGS assay for the identification of HER2 amplification, MSI status, MMR deficiency, TMB, and NTRK gene fusions, RET gene fusions, and BRAF V600E mutations when limited diagnostic tissue is available or patient can't undergo a traditional biopsy. 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 5 of 6)

The NCCN guideline for Ovarian Cancer Including Fallopian Tumor Cancer and Primary Peritoneal Cancer (2.2023) recommends that patients with recurrent disease, tumor molecular analysis have at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor specific or tumor-agnostic benefit. (p OV-6) More comprehensive testing may be particularly important in less common histologies with limited approved therapeutic options. (p. OV-B 1 of 3) These guidelines also recommend that molecular testing be performed on the most recent tumor tissue available. (p. OV-8)

The NCCN guideline for Pancreatic Adenocarcinoma (2.2023) recommends tumor/somatic molecular profiling for patients with local advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. They also recommend considering specifically testing for potentially actionable somatic findings including but not limited to

fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations *BRAF, BRCA1/2*, *KRAS*, *PALB2*, amplifications (*HER2*), MSI, and or mismatch repair deficiency. (p. PANC-1A)

The NCCN guideline for Prostate Cancer (3.2023) recommends for somatic tumor testing and that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. The guidelines also recommend that repeat tumor profiles can be considered at the time of progression of disease. They also recommend tumor testing for alterations in homologous recombination DNA report genes such as *BRCA1/2, ATM, PALB2, FANCA, RAD512D, CHEK2, CDK12*, is for patients with metastatic prostate cancer. (p. PROS-C 3 of 3)

Targeted RNA Fusion Panel Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2023) and Pediatric Acute Lymphoblastic Leukemia (1.2024) recommends comprehensive testing during the diagnostic workup by next generation sequencing for gene fusions and pathogenic mutations, especially for Ph-like ALL, which is associated with recurrent gene fusions in the tyrosine kinase pathways. Targeted testing for these abnormalities at diagnosis may aid in risk stratification. (p. ALL-1, p. PEDALL-1)) Per the NCCN Biomarker Compendium, testing for gene fusions involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, or PDGFRB and mutations involving FLT3, IL7R, SH2B3, JAK1, JAK3, and JAK2 (in combination with CRLF2 gene fusions) is recommended for this indication.

NCCN guidelines for Central Nervous System Cancers (1.2023) recommends NTRK fusion and BRAF fusion testing for glioblastoma, and ZFTA fusion testing for ependymomas by RNA sequencing for prognostication and treatment options. (p. BRAIN-E, 2, 5-6 of 9).

NCCN guidelines for Non-Small Cell Lung Cancer (3.2023) state that for patients who don't have identifiable driver oncogenes via broad panel testing, RNA-based NGS testing should be considered if not already performed, to maximize detection of fusion events as fusions involving ROS1, MET and RET have better detection using RNA based methods.(p. NSCL-H, 2, 4, 5 of 7).

NCCN guidelines for Soft Tissue Sarcoma (2.2023) state that while morphologic diagnosis remains the gold standard for 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 of 4).

NCCN guidelines for Histiocytic Neoplasms (1.2022) recommends molecular testing for somatic mutations and fusions in the workup for Langerhans Cell Histiocytosis, (p. LCH-1), Erdheim-Chester Disease, (p. ECD-1) and Rosai-Dorfman Disease (p. RDD-1). RNA-based molecular panel including fusion testing should cover BRAF, ALK, and NTRK1 rearrangements.

NCCN guidelines for Gastrointestinal Stromal Tumors (1.2023) state that all GIST lacking a KIT or PDGFRA mutation should be tested for alternative driver mutations (e.g., BRAF, NF1, NTRK, and FGFR fusions), which may be detected by NGS to identify potential targeted therapies. (p. GIST-B)

American Society of Clinical Oncology

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

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

Broad RNA Fusion Panel Tests

Stand-alone comprehensive RNA next-generation sequencing (NGS) testing for 51 or more RNA specific fusions is currently not supported by National Comprehensive Cancer Network (NCCN) guidelines or other oncology guidelines. Cancer-specific guidelines for RNA fusions are generally no more than 10 RNA fusion biomarkers. Therefore, stand-alone comprehensive RNA NGS testing for 51 or more RNA specific fusions is considered investigational for all indications.

Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (4.2023) recommends for patients over the age of 18 testing that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses. (p.EVAL-1) Multiplex gene panels and comprehensive next-generation sequencing (NGS)

analysis are recommended for the ongoing management of AML and various phases of treatment (p. EVAL-1A).

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2023) state that patients diagnosed with acute lymphoblastic leukemia should undergo molecular characterization including comprehensive testing by NGS for gene fusions and pathogenic mutations which may aid in risk stratification. (p. ALL-1). Additionally, patients who are undergoing surveillance after maintenance therapy and are showing evidence of symptomatic relapse should undergo repeat testing (p. ALL-6).

The NCCN guidelines for Myelodysplastic Syndromes (1.2023) recommends the following:

- Genetic testing for somatic mutations (i.e., acquired mutations) in genes associated with myelodysplastic syndromes should be performed for suspected myelodyplasia. (p. MDS-1)
- Additionally, patients who have persistent cytopenia (at least 4-6 months) and lack other underlying conditions that could cause cytopenia should be evaluated for myelodysplastic syndromes. (p. MDS-3)
- Several gene mutations have been identified among patients with MDS that may, in part, contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients. Such gene mutations will be present in the majority of newly diagnosed patients, including most patients with normal cytogenetics. (p. MS-18)
- Repeat molecular testing is recommended if a member/enrollee has relapsed after allo-HCT [hematopoietic cell transplant] (p. MDS-6 and MDS-6A)

The NCCN guidelines for Myeloproliferative Neoplasms (1.2023) recommend for patients suspected of having an MPN to have molecular testing for J*AK2* V617F*, CALR* and *MPL* mutations for patient with symptoms of essential thrombocythemia or myelofibrosis, and *JAK2* exon 12 mutations for patients with polycythemia vera. This testing can be done in a stepwise manner, or as an NGS multigene panel. (p. MPN-1.

The NCCN guidelines for Chronic Myeloid Leukemia (1.2024) indicate that a patient with advanced phase CML in either accelerated or blast phase should consider mutational analysis with a myeloid mutation panel (CML-1). Patients on TKI therapy who have progressed to accelerated or blast phase should consider a myeloid mutation panel to identify *BCR-ABL-1*-independent resistance mutations in patients with no BCR-ABL 1 kinase domain mutations. (p. CML-E)

Colorectal Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Colon Cancer (2.2023) recommends all patients with metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-B 4 of 8)

Lung Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Non-Small Cell Lung Cancer (3.2023) recommends at this time that when feasible, testing be performed via a broad, panel-based approach, most typically performed by NGS. For patients who, in broad panel testing do not have identifiable driver oncogenes (especially in never smokers), consider RNA-based NGS if not already performed, to maximize detection of fusion events. (p. NSCL-H 2 OF 7)

Cutaneous Melanoma Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Cutaneous Melanoma (2.2023) recommend *BRAF* and *KIT* testing, but broader genomic profiling (such as larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. (p. ME-C 4 of 8)

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panel

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (4.2023) recommends for patients over the age of 18 testing that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses including molecular analysis. (p.EVAL-1) Multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (p. EVAL-1A)

Myeloproliferative Neoplasms (MPNs) Panel Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (1.2023) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts be performed to exclude the diagnosis of CML. Additionally, molecular testing for *JAK2* mutations is recommended in initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MPN-1)

Tumor Specific *BCR/ABL1* Kinase Domain Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Chronic Myeloid Leukemia (1.2024) outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, including *BCR/ABL1* tests for diagnosis, monitoring, and *ABL* kinase domain single nucleotide variants. *BCR/ABL1* kinase domain mutation analysis is recommended, among other times, when patients fail to meet milestones related to disease response, the disease has progressed to the accelerated or blast phase, or there are clinical signs of loss of complete cytogenetic response. (p. CML-E)

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2023) recommend somatic genetic testing for all patients with ALL, as Ph-like ALL has a phenotype associated with recurrent gene fusions/mutations which may guide TKI treatment decision-making. (p. ALL-1 and ALL-1A) Similar recommendations are made in the NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (2.2023). (p. PEDALL-1 and PEDALL-1A)

Tumor Specific *BCR/ABL1* Quantitation and Breakpoint Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (2.2023) recommend that the presence of recurrent genetic abnormalities, specifically *BCR-ABL1* and *ETV6-RUNX1,* should be evaluated using karyotyping, FISH, or RT-PCR. They further recommend that if testing for those recurrent genetic abnormalities is negative, additional testing for recurrent genetic

abnormalities is encouraged in some patients and may aid in risk stratification. (p. PEDALL-1 and PEDALL-1A)

The NCCN guidelines on Acute Lymphoblastic Leukemia (2.2023) recommend that the presence of recurrent genetic abnormalities, specifically *BCR-ABL1*, should be evaluated using karyotyping, FISH, or RT-PCR. They further recommend that if testing for *BCR-ABL1* is negative, additional testing for recurrent genetic abnormalities associated with Ph-like ALL is essential. (p. ALL-1 and ALL-1A)

The NCCN guidelines on B-cell Lymphomas (5.2023) include PCR for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphoblastic lymphoma. (p. BLAST-1)

The NCCN guidelines for Myeloproliferative Neoplasms (3.2022) recommend evaluation for *BCR-ABL1* via FISH or multiplex RT-PCR to exclude a diagnosis of CML. (p. MPN-1)

The NCCN guidelines for Acute Myeloid Leukemia (4.2023) recommend BCR-ABL1 testing to assist in risk stratification of AML. (p. AML-A 1 of 4)

The NCCN guidelines for Chronic Myeloid Leukemia (1.2024) recommend quantitative RT-PCR testing for *BCR/ABL1* for patients undergoing work-up for CML. (p. CML-1)

Tumor Specific *BRAF* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Thyroid Carcinoma (3.2023) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS. Additionally, they comment that molecular testing has shown to be beneficial when making targeted therapy decisions. The guideline also comments that individuals with anaplastic thyroid cancer and/or metastatic disease should undergo molecular testing including *BRAF, NTRK, ALK, RET* and tumor mutational burden if not previously done. (p. ANAP-1, p. PAP-9, p. FOLL-8, p. HURT-8)

The NCCN guideline on Hairy Cell Leukemia (1.2023) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL[classical hairy cell leukemia]immunophenotype. (p. HCL-1)

The NCCN guideline on Cutaneous Melanoma (2.2023) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. (ME-C 4 of 8)

The NCCN guideline on Central Nervous System Cancers (1.2023) states that *BRAF* fusion and/or mutation testing is clinically indicated in patients with low-grade glioma or pilocytic astrocytoma. (p. GLIO-1)

The NCCN guidelines for Non-Small Cell Lung Cancer (3.2023) recommend molecular testing including *BRAF* analysis for advanced or metastatic adenocarcinoma, large cell, NSCLC not otherwise specified, or squamous cell carcinoma. (p. NSCL-18)

The NCCN guidelines for Colon Cancer (2.2023) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma. (p. COL-2)

Tumor Specific *BRCA1/2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (2.2023) recommends that all patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should have genetic risk evaluation and germline and somatic testing of *BRCA1* and *BRCA2* if not previously done. (p. OV-1) In addition to *BRCA1/2* testing, other methods for evaluating HR deficiency status (e.g., genomic instability, loss of heterozygosity) can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor specific or tumor-agnostic targeted therapy options exist. (p. OV-B 1 of 3)

The NCCN guideline on Prostate Cancer (3.2023) recommend evaluating tumor for alterations in homologous recombination DNA repair genes such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2* and *CDK12* in patients with metastatic prostate cancer and tumor testing for MSI-H and/or dMMR can be considered. (p. PROS-C, 3 of 3)

The NCCN guideline on Pancreatic Cancer (2.2023) recommends molecular profiling of tumor tissue for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), etc. (p. PANC-1 and PANC-1A)

American Society of Clinical Oncology (ASCO)

ASCO (2020) published the following recommendations for somatic and germline genetic testing for women diagnosed with ovarian cancer:

- All women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting. (Recommendation 1.2, p. 6)
- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results. (Recommendation 1.2, p. 6)
- Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer. (Recommendation 1.4, p. 6)
- First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing. (Recommendation 1.5, p. 6)
- Clinical decision making should not be made based on a variant of uncertain significance. (p. 2)
- Women with epithelial ovarian cancer should have testing at the time of diagnosis. (p. 2)

Tumor Specific *CALR* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (1.2023) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts is recommended to exclude the diagnosis of CML (p. MS-6). Additionally, they recommend that molecular testing for *JAK2* mutations is recommended in initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MS-7 and MPN-1)

Tumor Specific *CEBPA* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (4.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *EGFR* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Non-Small Cell Lung Cancer (3.2023) state that molecular testing for *EGFR* mutations should be performed when adjuvant TKI therapy is a consideration for NSCLC stage IB–IIIA, IIIB [T3,N2]. Testing should also be performed for advanced or metastatic disease preferably by broad molecular profiling (p. NSCL-18). While the testing process may be technically easier on a resection specimen, initial diagnostic biopsy specimens are also acceptable for testing for this indication. (p. NSCL-H, 3 of 7)

Tumor Specific *ESR1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (4.2023) recommend that post-menopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutation positive breast cancer that have progressed following one or two lines of endocrine therapy, including one line containing a CDK4/6 inhibitor, be considered for treatment with Elacestrant. (p. BINV-Q 6 of 14)

Tumor Specific *FLT3* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (4.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further

recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *IDH1* and *IDH2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (4.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications, including *IDH1/IDH2.* (p. EVAL-1)

The NCCN guideline on Central Nervous System Cancers (1.2023) states that *IDH* mutation testing (*IDH1* and *IDH2*) is required for the work-up for all gliomas. (p. BRAIN-F 2 of 10)

Tumor Specific *IGHV* Somatic Hypermutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (3.2023) state that molecular testing for the immunoglobulin heavy chain variable region gene (IGHV) is useful for prognostic and/or therapy determination. (p. CSLL-1)

The NCCN B-cell Lymphomas guidelines (5.2023) recommend IGHV sequencing for individuals with mantle cell lymphoma, (p. MANT-1) These guidelines also state that molecular analysis of immunoglobulin gene rearrangements can be useful under some circumstances for patients with post-transplant lymphoproliferative disorders. (p. PTLD-1)

The NCCN Primary Cutaneous Lymphomas guidelines (1.2023) state that flow cytometry or IGH gene rearrangement studies can be of use for patients with primary cutaneous B-cell lymphoma if adequate biopsy material is available. (p. CUTB-1)

Tumor Specific *JAK2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (3.2022) recommend molecular testing for *JAK2* mutations in the initial work-up for all patients with suspected MPN. They further

recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MS-7)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (2.2023) recommend that those with the Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2*, or *PDGFRB* and mutations involving *FLT3, IL7R, SH2B3, JAK1, JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. (p. ALL-1A)

The NCCN guidelines for Myelodysplastic Syndromes (1.2023) list JAK2 as a potentially mutated gene in MDS. (p. MDS-C 2 of 3)

Tumor Specific *KIT* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Cutaneous Melanoma (2.2023) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. They further recommend that if feasible, broader genomic profiling with NGS panels be performed in individuals with stage IV or recurrent melanoma especially if the test results could guide future treatment options. (p. ME-C, 4 of 8)

NCCN guidelines for Gastrointestinal Stromal Tumors (1.2023) recommend *KIT* mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor. (p. GIST-B)

The NCCN guideline on Acute Myeloid Leukemia (4.2023) recommends all patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. Presently, *c-KIT*, *FLT3*-ITD, *FLT3*-TKD, *NPM1*, *CEBPA* (biallelic), *IDH1*/*IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* alpha are included in this group. (p. MS-3)

The NCCN guidelines for Systemic Mastocytosis (4.2023) recommends that all patients presenting with signs or symptoms of mastocytosis undergo molecular testing for KIT mutations. (p. SM-1)

Tumor Specific *KRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (2.2023) all patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor. (p.COL-B 4 of 8)

The NCCN guideline on Non-Small Cell Lung Cancer (3.2023) strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. The following genes are recommended - *EGFR* mutation, *ALK*, *KRAS, ROS1, BRAF*, *NTRK1/2/3, METex14* skipping, *RET, ERBB2 (HER2).* (p. NSCL- 18)

American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and Association for Molecular Pathology (AMP)

ASCO, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology (2017) published the following recommendations for the use of molecular biomarkers for the evaluation of colorectal cancer:

- Patients with CRC considered for anti-*EGFR* therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4. (p. 193)
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification (p. 201)
- *BRAF* p.V600 mutational analysis should be performed in dMMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome. (p. 201)

- Clinicians should order MMR status testing in patients with CRCs for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. (p. 192)

- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors. (p. 192)

Tumor Specific *MGMT* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Central Nervous System Cancers (1.2023) states that MGMT promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade 3 and 4). MGMT promoter methylation confers a survival advantage in glioblastoma and is used for risk stratification in clinical trials. Patients with glioblastoma that is not MGMT promoter methylated derive less benefit from treatment with TMZ compared to those whose tumors are methylated. (p. BRAIN-E, 3 of 9)

Tumor Specific *MLH1* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Genetic/Familial High-Risk Assessment: Colorectal (2.2022) states that patients with colorectal or endometrial (uterine) cancer with tumors that show abnormal MLH1 IHC should have testing for MLH1 promoter methylation. Hypermethylation of the MLH1 promoter in these tumors has been associated with sporadic cancer, and not Lynch syndrome. (p. LS-A 1 of 8)

American Society of Clinical Oncology (ASCO)

ASCO (2015) endorsed the following guidelines related to MSI, *BRAF*, and MLH1 testing in the assessment of CRC:

- Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines. (p. 210)
- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of *BRAF* V600E mutation or analysis of methylation of the *MLH1* promoter should be carried out

first to rule out a sporadic case. If the tumor is MMR deficient and somatic *BRAF* mutation is not detected or *MLH1* promoter methylation is not identified, testing for germline mutations is indicated. (p. 210)

Tumor Specific *MPL* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Myeloproliferative Neoplasms (1.2023) recommends molecular testing (blood or bone marrow) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with essential thrombocythemia and myelofibrosis) and JAK2 exon 12 mutations (for patients, with polycythemia vera) or molecular testing using multigene NGS panel that includes JAK2, CALR, and MPL. (p. MPN-1)

Tumor Specific Microsatellite Instability (MSI) Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Colon Cancer (2.2023) recommend determination of tumor MMR and MSI in all individuals with colorectal cancer. (p. COL-B 4 of 8)

The NCCN guidelines for Uterine Neoplasms (2.2023) recommend MSI (among other studies) for patients with endometrial carcinoma. (p. ENDO-A 2 of 4)

The NCCN guideline on Gastric Cancer (1.2023) recommends MSI testing for all newly diagnosed gastric cancers. (p. GAST-1)

The NCCN guideline on Esophageal and Esophagogastric Junction Cancer (2.2023) recommends MSI by PCR or NGS for patients with locally advanced, recurrent, or metastatic esophageal and EGJ cancers. (p. ESOPH-B 4 of 6)

The NCCN guidelines for Cervical Cancer (1.2023) recommend MSI testing for patients with progressive, recurrent, or metastatic disease. (p. CERV-A 1 of 3)

The NCCN guideline for Testicular Cancer (1.2023) recommends MSI testing in individuals with nonseminoma testicular cancer who have had progression after high-dose chemotherapy or third line therapy. (p. TEST-15)

The NCCN guidelines for Biliary Tract Cancers (2.2023) recommends MSI testing for unresectable or metastatic gallbladder cancer (p. GALL-5) or unresectable or metastatic

intrahepatic cholangiocarcinoma (p. INTRA-1) or extrahepatic cholangiocarcinoma. (p. EXTRA-1)

The NCCN guidelines for Breast Cancer (4.2023) can be considered for patients with unresectable or metastatic breast cancer when considering pembrolizumab as treatment. (p. BINV-R 1 of 3)

The NCCN guidelines for Small Bowel Adenocarcinoma (1.2023) recommend universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma. (p. SBA-B)

The NCCN guidelines for an Occult Primary (3.2023) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology. (p. OCC-1)

The NCCN guidelines for Pancreatic Adenocarcinoma (2.2023) recommend MSI (among other studies) for patients with metastatic pancreatic cancer. (p. PANC-1A)

Tumor Specific *NPM1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (4.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *NRAS* Variant Analysis

American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and Association for Molecular Pathology (AMP)

ASCO, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology (2017) published the following recommendations for the use of molecular biomarkers for the evaluation of colorectal cancer:

- Patients with CRC considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4. (p.193)
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification. (p. 201)
- *BRAF* p.V600 mutational analysis should be performed in dMMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome. (p. 201)
- Clinicians should order MMR status testing in patients with CRCs for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. (p. 192)

- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors. (p. 192)

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (2.2023) recommends that all patients with metastatic colorectal cancer should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel. (p. COL-B 4 of 8)

Tumor Specific *PIK3CA* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (4.2023) recommends that recurrent or stage IV HR-positive/HER2-negative breast cancers be assessed for PIK3CA mutations with tumor or liquid biopsy to identify candidates for Alpelisib + fulvestrant. They also recommend that recurrent or stage IV MSH-H/dMMR breast cancers that have progressed following prior treatment be considered for treatment with Pembrolizumab. (p. BINV-R 1 of 3)

The NCCN guidelines on Uterine Neoplasms (2.2023) state that *PIK3CA* mutations can be found in pleomorphic uterine rhabdomyosarcomas. (p. UTSARC-A 7 of 8)

Tumor Specific *TP53* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (4.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while

other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

The NCCN guidelines on B-cell Lymphoma (5.2023) recommend *TP53* mutation analysis for patients with a diagnosis of mantle cell lymphoma in order to direct treatment selection, as patients with a *TP53* mutation have been associated with poor prognosis when treated with conventional therapy. (p. MANT-1)

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (3.2023) recommend *TP53* sequencing analysis and *IGHV* mutation analysis to inform prognosis and therapeutic options for patients diagnosed with CLL/SLL or upon progression or recurrence (p. CSLL-1). Minimal residual disease testing at the end of treatment for CLL is recommended. (p. CSLL-2, 2 of 2)

MEASUREABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS

Hematologic Minimal Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2023) recommend baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis (p. ALL-1). After treatment induction, MRD is recommended to determine consolidation therapy (p. ALL-3). For surveillance on bone marrow aspirate, MRD assessment is recommended. (p. ALL-6)

The NCCN guidelines for Multiple Myeloma (3.2023) recommend consideration of MRD testing by NGS in the initial diagnostic workup (p. MYEL-1) or follow up/surveillance, prognostication. (p. MYEL-4)

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (3.2023) recommend minimal residual disease testing at the end of treatment for CLL/SLL. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method. (p. CSLL-E 1 of 2)

Solid Tumor Minimal Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)

Per the NCCN Colon Cancer guidelines (2.2023), "There is currently insufficient evidence to recommend routine use of circulating tumor DNA (ctDNA) assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results. Participation in clinical trials is encouraged." (p. COL-4)

The Colon Cancer guidelines also add that "...the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy." (MS-22)

The NCCN Breast Cancer guidelines (4.2023) state the following: "The clinical use of Circulating Tumor Cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring. (p. MS-75)

None of the NCCN guidelines currently recommend performing minimal residual disease (MRD) testing as part of monitoring for recurrence of solid tumors.

Tumor Mutational Burden (TMB)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Breast Cancer (4.2023) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. BINV-R 1 of 3)

The NCCN guidelines for Cervical Cancer (1.2023) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. CERV-F 1 of 3)

The NCCN guidelines for Biliary Tract Cancers (2.2023) recommend tumor mutational burden testing for unresectable or metastatic gallbladder cancer. (p. GALL-5) These guidelines also recommend tumor mutational burden testing for unresectable or metastatic intrahepatic cholangiocarcinoma (p. INTRA-1) and unresectable or metastatic extrahepatic cholangiocarcinoma. (p. EXTRA-1)

The NCCN guidelines for Occult Primary Cancers (3.2023) recommends consideration of tumor mutational burden testing for patients with suspected metastatic malignancy of uncertain pathology. (p. OCC-1)

The NCCN guidelines for Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (2.2023) recommend tumor analysis, including tumor mutational burden, for recurrent ovarian/Fallopian tube/primary peritoneal cancer. (p. OV-B 1 of 3)

The NCCN guidelines for Pancreatic Adenocarcinoma (2.2023) recommend testing tumor mutational burden for patients with locally advanced and metastatic pancreatic cancer as pembrolizumab may be considered for treatment. (p. PANC-F 6 of 9)

The NCCN guideline for Prostate Cancer (3.2023) states that tumor mutational burden testing may be considered for patients with metastatic castration-resistant prostate cancer. (p. PROS-C 3 of 3)

The NCCN guidelines for Testicular Cancer (1.2023) recommend tumor mutational burden testing for patients with nonseminoma testicular cancer who have experienced disease progression after high-dose chemotherapy or third-line therapy. (p. TEST-15)

The NCCN guidelines for Uterine Neoplasms (2.2023) recommend consideration of tumor mutational burden testing for patients with endometrial cancer (p. ENDO-A 2 of 4). The guidelines also recommend tumor mutational burden testing be done for patients with uterine sarcoma. (p. UTSARC-A 1 of 8)

Red Blood Cell Genotyping in Multiple Myeloma

Association for the Advancement of Blood and Biotherapies

The AABB (Association for the Advancement of Blood and Biotherapies; formerly known as the American Association of Blood Banks) published Association Bulletin #16-02 on January 15, 2016 (updated July 2022) recommending that all patients should undergo baseline phenotype and genotype prior to initiation of anti-CD38 monoclonal antibody treatment (daratumumab) to mitigate the potential of anti-CD38 interference with serologic testing. The bulletin also notes that this genotyping can be performed after the initiation of treatment. (p. 2 and 3)

Cancer Exome and Genome Sequencing

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

Genetic Testing to Confirm the Identity of Laboratory Specimens

None of the National Comprehensive Cancer Network (NCCN) guidelines currently recommend or address performing separate genetic testing to confirm the identity of laboratory specimens.

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: removed "comprehensive". For Other Related Policies: added "and Molecular". For Criteria; under Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests: I. removed "81449…"; added "81455…"; II. removed "81449…"; added "81455"; removed"0211U…"; added "0379U"; II.A.1. removed "Metastatic colon cancer, OR"; II.A.4. removed "OR"; III. Removed "81449…"; added "0250U…"; removed Tumor Type Agnostic Solid Tumor Molecular Profiling Panel Tests with IHC and Cytogenic Analyses and related criteria; added Targeted RNA Fusion Panel Tests and related criteria; added Broad RNA Fusion Panel Tests and related criteria; under Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels: I. replaced "Comprehensive" with "Broad"; removed I.B. "myelodysplastic…"; I.B. added "acute lymphoblastic…"; I.C. added "The member/enrollee has newly diagnosed…"; I.D. added "The member/enrollee has suspected…"; I.E. added "The member/enrollee is suspected to have…"; I.E.2. added "Previous results of"; removed "previously performed…"; I.F. added "(CML)"; I.F.2. removed "Comprehensive"; added "were negative"; added II. "Repeat broad molecular…"; III. Added "Broad"; under Colorectal Cancer Focused Molecular Profiling Panels: I.A. removed "synchronous or metachronous"; I.C. added "The panel contains…"; under Cutaneous Melanoma Focused Molecular Profiling Panels: I. and II. removed "81210, 81404"; for Myeloproliferative Neoplasms (MPNs) Panel Tests: I. and II. added "81279"; under Tumor Specific *BCR/ABL1* Kinase Domain Analysis: I. replaced "ABL" with "ABL1"; under Tumor Specific *BCR/ABL1* Quantitation and Breakpoint Analysis: I.B. added "(i.e., for minimal residual…)"; under Tumor Specific *BRAF* Variant Analysis: I.A.1. removed "synchronous or metachronous"; under Tumor Specific *BRCA1/2* Variant Analysis: I.A.2. added "OR"; I.A.3. added "Locally advanced/metastatic…"; under Tumor Specific *EGFR* Variant Analysis:I.A.1-I.A.4. replaced "Advanced or metastatic" with "Stage IB or higher"; under Tumor Specific *IDH1* and *IDH2* Variant Analysis: I.B. added "AML"; under Tumor Specific *JAK2* Variant Analysis: I.A. added "(MPN)"; I.B. added "(ALL)"; I.C. added "(MDS)"; under Tumor Specific *KIT* Variant Analysis: I.B. added "(AML)"; under Tumor Specific *KRAS* Variant Analysis: I.A. added "meets one of the following:"; I.A.2.	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
added "The member/enrollee"; removed "synchronous or unresectable metachronous"; removed II. "Somatic KRAS variant analysis…"; under Tumor Specific Microsatellite Instability (MSI) Analysis: I.A.6. replaced "and has had" with "with"; added I.A.11. "Metastatic pancreatic cancer, OR"; under Tumor Specific *NRAS* Variant Analysis: I.A. removed "synchronous or metachronous"; under Tumor Specific *PIK3CA* Variant Analysis: I.A. added "a diagnosis of"; under Tumor Specific *TP53* Variant Analysis: I. replaced "RET" with "TP53"; removed "(81404, 81405…"; added "81352…"; I.A. removed "medullary thyroid…"; added "acute myeloid…"; added I.B. "The member/enrollee has a diagnosis…"; added Solid Tumor Minimal Residual Disease (MRD) Testing with related criteria; under TUMOR MUTATIONAL BURDEN (TMB): I.A.4. added "or intrahepatic"; I.A.9. added "chemotherapy"; under Cancer Exome and Genome Sequencing: I. replaced "0329U" with "0297U"; under Genetic Testing to Confirm the Identity of Laboratory Specimens: I. removed "0079U"; removed table "Medically Necessary Tumor Testing by Cancer Types. For Notes and Definitions: added 4. "Myelodysplastic Syndromes…". For Background and Rationale: removed "trastuzumab therapy…"; added "an FDA approved therapy…"; removed "Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels and related content; added Targeted RNA Fusion Panel Tests and related content; removed Tumor Type Agnostic Solid Tumor Molecular Profiling Panel Tests with IHC and Cytogenic Analyses and related content; added Broad RNA Fusion Panel Tests and related content; added Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels and related content; under Myeloproliferative Neoplasms (MPNs) Panel Tests: replaced "is recommended" with "be performed"; removed "they recommend that"; under Tumor Specific *BRCA1/2* Variant Analysis: added "The NCCN guideline on Pancreatic Cancer…"; under Tumor Specific *EGFR* Variant Analysis: added "IIIB…"; under Tumor Specific *ESR1* Variant Analysis: added "National Comprehensive Cancer Network (NCCN)"; added "positive"; under Tumor Specific *JAK2* Variant Analysis: removed "that FISH or RT-PCR…"; under Tumor Specific *MGMT* Methylation Analysis: removed "recommends molecular testing…"; added "states that MGMT promoter…"; under Tumor Specific Microsatellite Instability (MSI) Analysis: replaced "Hepatobiliary" with "Biliary Tract"; added "The NCCN guidelines…"; under Tumor Specific *PIK3CA* Variant Analysis: removed "uterine neoplasms…"; removed Tumor Specific RET Variant Analysis and related content; added Solid Tumor Minimal Residual Disease (MRD) Analysis and related content; under Tumor Mutational Burden (TMB): replaced "Hepatobiliary" with "Biliary tract."		
Added CPT code 0422U to the policy reference table and criteria for Solid Tumor Minimal Residual Disease (MRD) Testing. Added CPT codes 81457, 81458, 81459 to criteria for Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests.	11/23	

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3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.