ONCOLOGY: MOLECULAR ANALYSIS OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

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 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.

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

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.

POLICY REFERENCE TABLE

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

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies				
Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels	FoundationOne CDx (Foundation Medicine)	0037U	C00-D49, Z85	1, 2, 4, 5, 7, 14, 23, 24, 29, 36, 40
	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, 81457, 81458		
	Tempus xT (Tempus)			
	Precise Tumor (Myriad)			
	Guardant360 TissueNext (Guardant)	0334U		
	PGDx elio tissue complete (Personal Genome Diagnostics, Inc)	0250U		

	OmniSeq INSIGHT (Labcorp)	81455		
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)			
	Solid Tumor Expanded Panel (Quest Diagnostics)	0379U		
	UW OncoPlex Cancer Gene Panel (University of Washington)	81459		
	Strata Select (Strata Oncology)	0391U		
Targeted RNA Fusion Panels	Targeted Solid Tumor NGS Fusion Panel (NeoGenomics)	81449, 81451	C91, C34, C71, C49, C96	1, 8, 17, 20, 33, 37, 38, 39
Broad RNA Fusion Panels	Tempus xR Whole Transcriptome RNA Sequencing (Tempus)	81456	C00-C80	16, 17
	Aventa FusionPlus (Aventa Genomics)	0444U		
Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81450, 81455	C91, C92, D46.9	6, 10, 12, 15, 17
	Tempus xT Hematologic Malignancy (Tempus)			
	Neo Comprehensive - Myeloid Disorders (NeoGenomics Laboratories)			
	MayoComplete Myeloid Neoplasms, Comprehensive OncoHeme Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)	81450		
	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		

	COLONSEQPlus Panel (MedFusion)	81457		
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test (Thermo Fisher Scientific)	0022U	C34	1
	OnkoSight Advanced Lung Cancer NGS Panel (BioReference Laboratories)	81457		
Cutaneous Melanoma Focused Molecular Profiling Panels	MelanomaSeqPlus (Quest Diagnostics)	81445	C43, D03	9
	OnkoSight Advanced Melanoma NGS Panel (BioReference Laboratories)	81457		
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML NGS Gene Panel Assay (Laboratory for Personalized Molecular Medicine)	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* FISH, Qualitative,and Quantitative Tests	BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics)	81206, 81207, 81208	C83, C85, C91.00 - C91.02, C92.0 - C92.12, D45, D47, D47.1,	10, 12, 15, 16, 17, 18
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative			

	(Labcorp)		D47.3, D69.3	
	BCR/ABL1 (t9;22)) RNA Quantitative with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology)	0016U		
	MRDx BCR-ABL Test (MolecularMD)	0040U		
	Detection by FISH of t(9;22) BCR/ABL (CGC Genetics)	81479, 88271, 88274, 88275, 88291		
	BCR/ABL t(9;22) (NeoGenomics Laboratories)			
	BCR ABL Qualitative (Cincinnati Children's Hospital)			
Tumor Specific *BRAF* Variant Analysis	BRAF Mutation Analysis (NeoGenomics)	81210	C18-C21, C34, C43, C71, C73, C91.4	1, 2, 7, 9, 13, 19, 20, 32, 36
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, 21, 23
	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	FLT3 ITD and TKD Mutation (PCR) (PathGroup)	81245, 81246	C92	

Analysis	LeukoStrat CDx FLT3 Mutation Assay (Versiti)	0023U		6, 10, 12, 16, 17
	FLT3 ITD MRD Assay (Laboratory for Personalized Molecular Medicine)	0046U		
Tumor Specific *IDH1* and *IDH2* Variant Analysis	IDH1/IDH2 Mutation Analysis by PCR (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, 26, 34
Tumor Specific *JAK2* Variant Analysis	JAK2 Exon 12 to 15 Sequencing, Polycythemia Vera Reflex, Varies (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 in Systemic Mastocytosis (Labcorp)			
Tumor Specific *KRAS* Variant Analysis	KRAS Mutation Analysis (NeoGenomics)	81275, 81276	C18-21, C34	1, 2, 7
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, 22
Tumor Specific *MPL* Variant Analysis	MPL Mutation Analysis (Quest Diagnostics)	81338, 81339	D45, D47.1, D47.3, D75.81	12
Tumor Specific Microsatellite	Microsatellite Instability (MSI) by PCR (NeoGenomics)	81301	C15-C23, C50, C53,	2, 4, 7,14,

Instability (MSI) Analysis	Microsatellite Instability (MSI) (Quest Diagnostics)		C54.1, C62, C80	24, 25, 27, 28, 29, 30 32, 39
Tumor Specific *NPM1* Variant Analysis	NPM1 MRD Assay (Laboratory for Personalized Molecular Medicine)	0049U	C92	10
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)	81310		
Tumor Specific *NRAS* Variant Analysis	NRAS Mutation Analysis (NeoGenomics)	81311	C18-C21	2
Tumor Specific *PIK3CA* Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309	C50, C55	4, 14
	PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp)	0155U		
Tumor Specific *TP53* Variant Analysis	TP53 Mutation Analysis (NeoGenomics Laboratories)	81352	C92, R71, R79	10, 18, 26
Measurable (Minimal) Residual Disease (MRD) Analysis				
Hematologic Minimal Residual Disease (MRD) Analysis	MyMRD NGS Panel Assay(Laboratory for Personalized Molecular Medicine)	0171U	C91, R71, R79	17, 26, 31
	ClonoSEQ Assay (Adaptive Biotechnologies)	0364U		
Solid Tumor Minimal Residual Disease (MRD) Analysis	Signatera - Residual Disease Test (MRD) - (Natera)	0340U	C00-D49, Z85	2, 4
	Personalized Cancer MonitoringBaseline Test (Invitae)	0306U		
	Personalized Cancer Monitoring - Monitoring TestD (Invitae)	0307U		
	RaDaR (NeoGenomics)	81479		
	Colvera (Clinical Genomics Pathology)	0229U		
	Guardant360 Response (Guardant Health)	0422U		

Tumor Mutational Burden (TMB)				
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479	C00-D49, Z85	4, 5, 7, 13, 14, 23, 24, 25, 28, 29, 30, 32, 39, 40, 41, 42, 43
Red Blood Cell Genotyping in Multiple Myeloma				
Red Blood Cell Genotyping in Multiple Myeloma	PreciseType HEA (Immucor)	0001U	C90.0, R71, R79	35
	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	33
	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	33

OTHER RELATED POLICIES

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

- ***Oncology: Cytogenetic Testing*** for coverage 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 coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology: Cancer Screening*** for coverage 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 coverage 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 coverage criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to tumor and hematologic malignancy testing that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

I. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **medically necessary** when:

   A. The member has a diagnosis of:

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

      2. Histiocytosis**, OR**

      3. Non-small cell lung cancer (NSCLC) regardless of stage, **AND**

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

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

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

   D. The member has resectable or borderline resectable pancreatic adenocarcinoma, **AND**

      1. The member is being considered for systemic therapy.

II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) is considered **medically necessary** when:

   A. The member has progression of:

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

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

      3. Metastatic prostate cancer.

III. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **investigational** for all other indications.

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

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Targeted RNA Fusion Panels

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

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

1. Adult or pediatric acute lymphoblastic leukemia (ALL), **OR**
2. Glioma, **OR**
3. Histiocytosis, **OR**
4. Sarcoma, **OR**

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

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

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

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

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

1. There is a fusion-targeted therapy with regulatory approval for that cancer type, **OR**
2. DNA-based panel testing was negative for oncogenic driver mutations.

II. RNA specific fusion panels (81449, 81451) are considered **investigational** for all other indications.

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Broad RNA Fusion Panels

I. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) are considered **medically necessary** when:

   A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL).

II. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) are considered **investigational** for all other indications.

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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 has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML), **OR**

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

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

   D. The member has suspected myelodysplastic syndrome (MDS) **AND**

      1. Other causes of cytopenia(s) have been ruled out, **OR**

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

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

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

F. The member 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 has myelodysplastic syndrome (MDS), **AND**

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

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

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

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

1. The member 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, 81457) in solid tumors are considered **medically necessary** when:

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

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

II. Colorectal cancer-focused molecular profiling panels (0111U, 81445, 81457) 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, 81457) are considered **medically necessary** when:

   A. The member has a diagnosis of:

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

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

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

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

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

II. Repeat lung cancer-focused molecular profiling panels (0022U, 81457) are considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer.

III. Lung cancer-focused molecular profiling panels (0022U, 81457) 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, 81457) are considered **medically necessary** when:

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

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

   C. One of the following:

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

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

II. Cutaneous melanoma focused molecular profiling panels (81445, 81457) 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 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) are 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) Panels

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

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

B. The member has any of the following:

1. Inadequate initial response to TKI therapy, **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* FISH, Qualitative, or Quantitative Tests

I. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 88271, 88274, 88275, 88291, 81479) in hematologic malignancies is considered **medically necessary** when:

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

B. The member is undergoing diagnostic workup for:

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

C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for:

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 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**
7. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma, **OR**
8. Metastatic small bowel adenocarcinoma, **OR**

B. The member is being evaluated for:

1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype), **OR**
2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).

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Tumor Specific *BRCA1/2* Variant Analysis

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

A. The member has a diagnosis of:

1. Ovarian, fallopian tube and/or primary peritoneal cancer, **OR**
2. Metastatic prostate cancer, **OR**
3. Resectable, borderline resectable, or 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 is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).

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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 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 has a diagnosis of:

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

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Tumor Specific *ESR1* Variant Analysis

I. Tumor specific *ESR1* variant analysis (81479) in solid tumors is considered **medically necessary** when:

A. The member is a postmenopausal female or adult male, **AND**

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

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

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Tumor Specific *FLT3* Variant Analysis

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

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

B. The member has a diagnosis of

1. Acute lymphocytic leukemia (ALL), **OR**
2. Myelodysplastic syndrome (MDS), **OR**
3. Myeloproliferative neoplasm.

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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 has a diagnosis of:

1. Glioma, **OR**
2. 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 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 is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**

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

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

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

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

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

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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 has suspected or proven metastatic colorectal cancer, **OR**

B. The member is undergoing workup for metastasis of non-small cell lung cancer, **OR**

C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.

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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 has a diagnosis of:

1. High grade (stage III or IV) anaplastic oligodendroglioma, **OR**
2. High grade (stage III or IV) anaplastic astrocytoma, **OR**
3. High grade (stage III or IV) anaplastic glioma, **OR**
4. High grade (stage III or IV) 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 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 is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).

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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 has a diagnosis of:

1. Colorectal cancer, **OR**
2. Endometrial cancer, **OR**
3. Gastric cancer, **OR**
4. Esophageal and esophagogastric junction cancer, **OR**
5. Recurrent, progressive or metastatic cervical carcinoma, **OR**
6. Testicular cancer (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. Resectable, borderline resectable, or metastatic pancreatic cancer, **OR**

12. Metastatic occult primary, **OR**

13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva**.**

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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 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 has suspected or proven metastatic colorectal cancer.

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Tumor Specific *PIK3CA* Variant Analysis

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

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

B. The member 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 has a diagnosis of:

1. Acute myeloid leukemia (AML), **OR**
2. Chronic lymphocytic leukemia (CLL), **OR**
3. Small lymphocytic leukemia (SLL), **OR**

B. The member 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 considered **medically necessary** when:

A. The member has a diagnosis of:

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

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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 has a diagnosis of:

1. Recurrent or metastatic breast cancer, **OR**
2. Unresectable or metastatic gallbladder cancer, **OR**
3. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma, **OR**
4. Suspected metastatic malignant occult primary tumor, **OR**
5. Recurrent ovarian/fallopian tube/primary peritoneal cancer, **OR**
6. Resectable or borderline resectable or metastatic or advanced pancreatic adenocarcinoma, **OR**
7. Metastatic castration-resistant prostate cancer, **OR**
8. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy, **OR**
9. Endometrial carcinoma or uterine sarcoma, **OR**
10. Locally advanced/metastatic ampullary adenocarcinoma, **OR**
11. Metastatic chondrosarcoma, **OR**
12. Metastatic chordoma, **OR**
13. Widely metastatic Ewing sarcoma, **OR**
14. Metastatic osteosarcoma, **OR**
15. Metastatic esophageal or esophagogastric junction cancer, **OR**

16. Gastric cancer, **OR**
17. Metastatic salivary gland tumor, **OR**
18. Adrenocortical carcinoma, **OR**
19. Extrapulmonary poorly differentiated neuroendocrine carcinoma, **OR**
20. Neuroendocrine large or small cell carcinoma, **OR**
21. Mixed neuroendocrine-non-neuroendocrine neoplasm, **OR**
22. Structurally persistent/recurrent locoregional or distant metastatic papillary thyroid carcinoma, **OR**
23. Structurally persistent/recurrent locoregional or distant metastatic follicular thyroid carcinoma, **OR**
24. Structurally persistent/recurrent locoregional or distant metastatic oncocytic thyroid carcinoma, **OR**
25. Stage IV anaplastic carcinoma, **OR**
26. Vulvar squamous cell carcinoma, **OR**
27. Metastatic small bowel adenocarcinoma.

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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 has a diagnosis of multiple myeloma, **AND**

   B. The member 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., know error) (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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DEFINITIONS

1. **Tumor mutational burden:** A measurement of mutations carried by tumor cells and is a predictive biomarker that is being studied to evaluate its association with response to immunotherapy.
2. **Advanced cancer:** 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:** 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):** 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)

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

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BACKGROUND AND RATIONALE

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (1.2024) recommend comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer. (p. BINV-18)

The NCCN guideline on Occult Primary (1.2024) 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 (2.2024) has several recommendations regarding biomarker testing:

- For stage IV / advanced or metastatic disease, molecular testing should include *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3*, *MET*ex14 skipping, *RET, ERBB2 (HER2),* and *PD-L1*. Broad molecular profiling is recommended to be performed. (p. NSCL-14, NSCL-19).
- Generally, it is recommended that broad, panel-based genomic profiling be performed via NGS when feasible. NCCN defines broad molecular profiling as a panel which includes all of the following biomarkers in either one assay or several smaller assays: *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3*, *MET*ex14 skipping, *RET, ERBB2 (HER2),* and *PD-L1*. (p. NSCL-20 and NSCL-H 1 and 2 of 8)
- Repeat somatic genetic testing can be helpful to aid in deciding next therapeutic steps when a patient's tumor shows evidence of progression on first-line therapy. Broad genomic profiling may be the best testing method to ensure all possible therapeutic biomarkers are analyzed (p. NSCL-H 7 of 8)

The NCCN guideline for Colon Cancer (1.2024) 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 (3.2023) 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 (1.2024) 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 (1.2024) recommends tumor/somatic molecular profiling for patients with resectable or borderline resectable,

or 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, PANC-F, 1 of 12)

The NCCN guideline for Prostate Cancer (4.2023) recommends somatic tumor testing and states 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)

The NCCN guideline for Histiocytic Neoplasms (1.2023) recommends targeted-capture, next generation sequencing (NGS) in the work-up/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD). or both LCH and ECD, NCCN notes that molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. (p. LCH-2, ECD-2 For RDD, NCCN recommends targeted-capture, next-generation sequencing (NGS) for mutations in the MAPK pathway and in other molecular pathways. (p. RDD-1)

The NCCN guideline for Uterine Neoplasms (1.2024) states that comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a clinical laboratory improvement amendment (CLIA)-certified laboratory, in the initial evaluation of uterine neoplasms. (p. ENDO-A 2 of 4)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend somatic molecular profiling for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy. Testing on tumor tissue is preferred but cell-free DNA testing can be considered if tumor tissue testing is not feasible. (p. AMP-6)

Targeted RNA Fusion Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) and Pediatric Acute Lymphoblastic Leukemia (3.2024) 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 (2.2024) 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 (3.2023) 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 (1.2023) 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 panels 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 Panels

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) state that comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended at the time of diagnosis. (p. ALL-1)

The NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (3.2024) recommend assessment of various potentially actionable or prognostic mutations and gene fusions via next generation sequencing (NGS) or alternative methods at the time of diagnosis. (p. PEDALL-1)

Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (6.2023) recommends testing for patients over the age of 18 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 (3.2023) 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 (3.2023) recommends the following:

- Genetic testing for somatic mutations (i.e., acquired mutations) in genes associated with myelodysplastic syndromes should be performed for suspected myelodysplasia. (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 has relapsed after allo-HCT [hematopoietic cell transplant]. (p. MDS-6 and MDS-6A)

The NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommend for patients suspected of having an MPN to have molecular testing for *JAK2* 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 (2.2024) 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-ABL1* kinase domain mutations. (p. CML-E)

Colorectal Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Colon Cancer (1.2024) recommends all patients with suspected or proven metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-2) The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types. (p. COL-B, 4 of 8) In addition, patients with documented metachronous metastases

should have determination of tumor gene status for *RAS* and *BRAF* mutations. (p. COL-9)

The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS, NRAS,* and *BRAF* mutations are similar in both specimen types.

Lung Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for Non-Small Cell Lung Cancer (2.2024) 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 (3.2023) state that *BRAF* and *KIT* testing should be performed for initial presentation with stage IV disease or clinical recurrence, 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. If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, *KIT*, *BRAF* non-V600). (p. ME-C 4 of 8)

Repeat molecular testing upon recurrence or metastasis is likely to be of low yield, unless new or more comprehensive testing methods are used or a larger, more representative sample is available if there is concern for sampling error. Repeat testing following progression on targeted therapy (*BRAF*- or *KIT*-directed therapy) does not appear to have clinical utility, since the mechanisms of resistance are diverse and do not have prognostic or therapeutic relevance. (p. ME-C 5 of 8)

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (6.2023) 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) Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (3.2023) 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 (2.2024) outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, including *BCR/ABL1* tests for diagnosis, monitoring, and *ABL1* 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 (3.2023) recommend *ABL1* kinase domain mutation testing for patients with relapsed/refractory, Philadelphia chromosome positive (Ph+) B-ALL. (p. ALL-9, p. ALL-1) Similar recommendations are made in the NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (3.2024). (p. PEDALL-1 and PEDALL-1A)

Tumor Specific *BCR/ABL1* FISH, Qualitative and Quantitative Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (3.2024) recommend reverse transcriptase-polymerase chain reaction (RT-PCR) testing for *BCR*::*ABL1* (quantitative or qualitative) in B-ALL including determination of transcript size (ie, p190 vs. p210). If *BCR*::*ABL1* negative: encourage testing for gene fusions and mutations associated with *BCR*::*ABL1*–like (Ph-like) ALL to aid in risk stratification. (p. PEDALL-1 and PEDALL-1A)

The NCCN guidelines on Acute Lymphoblastic Leukemia (3.2023) recommend reverse transcriptase polymerase chain reaction (RT-PCR) testing for *BCR*::*ABL1* in B-ALL (quantitative or qualitative), including determination of transcript size (ie, p190 vs. p210). (p. ALL-1)

The NCCN guidelines on B-cell Lymphomas (1.2024) 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 (1.2024) 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 (6.2023) recommend *BCR-ABL1* testing to assist in risk stratification of AML in the evaluation and initial workup for suspected AML. AML with *BCR-ABL1* rearrangement is a rare de novo AML that may benefit from therapies that entail tyrosine kinase inhibitors. (p. AML-A 1 of 4, MS-3, MS-4, MS-6)

The NCCN guidelines for Chronic Myeloid Leukemia (2.2024) 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 (4.2023) 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 (1.2024) 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 (3.2023) 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 (1.2024) 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 (1.2024) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma. (p. COL-2)

NCCN guidelines for Histiocytic Neoplasms (1.2023) recommends *BRAF* V600E testing (IHC or PCR) from biopsy tissue during the workup for Langerhans cell histiocytosis or Erdheim-Chester disease. (p. LCH-1, ECD-1)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) indicate that testing for potentially actionable somatic findings including *BRAF* mutations should be considered

for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-C, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

NCCN guidelines for Small Bowel Adenocarcinoma (1.2024) recommend *BRAF* V600E testing for metastatic adenocarcinoma (p. SBA-5)

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 (1.2024) 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 (4.2023) 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 (1.2024) recommends molecular profiling of tumor tissue for patients with resectable, borderline resectable, or 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)

Tumor Specific *CALR* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) state 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 (6.2023) 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 (2.2024) 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 (1.2024) 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 (6.2023) 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)

NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) and Pediatric Acute Lymphoblastic Leukemia (3.2024) indicate that comprehensive testing for gene fusions and pathogenic mutations using NGS sequencing is recommended for molecular prognostic risk stratification and that *FLT3* mutations confer poor or unfavorable risk. (p. ALL-1, ALL-3, PEDALL-1, PEDALL-A, 1 of 2)

The NCCN guidelines on Myelodysplastic Syndromes (3.2023) highly recommends genetic testing for somatic mutations in genes associated with myelodysplastic syndromes, which includes *FLT3* (p. MDS-1, MDS-C, 1 of 3).

NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommends NGS panel for mutational prognostication in patients with confirmed MPN diagnosis. (p. MPN1) Based on NGS panel results (e.g., if NGS shows particular mutations such as *IDH1*, *IDH2*, or *FLT3*), low intensity or targeted therapy can be considered. (p. MS-30)

Tumor Specific *IDH1* and *IDH2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (6.2023) 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 (1.2024) 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 (1.2024) 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 (1.2024) 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 (1.2024) 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 (3.2024) 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 (3.2023) 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 (3.2023) 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 (6.2023) 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 (1.2024) 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 (1.2024) 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 (2.2024) 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)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) indicate that testing for potentially actionable somatic findings including *RET* fusions should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-C, 1 of 12) as well as in locally advanced/metastatic disease (p. PANC-1A).

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 (2.2023) 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 (1.2024) 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 (1.2024) 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 (1.2024) recommend MSI (among other studies) for patients with endometrial carcinoma. (p. ENDO-A 2 of 4)

The NCCN guideline on Gastric Cancer (3.2023) recommends MSI testing for all newly diagnosed gastric cancers. (p. GAST-1)

The NCCN guideline on Esophageal and Esophagogastric Junction Cancer (4.2023) recommends MSI by PCR or NGS for all patients with newly diagnosed esophageal and EGJ cancers. (p. ESOPH-B 4 of 6)

The NCCN guidelines for Cervical Cancer (1.2024) 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 (3.2023) 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 (1.2024) 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 (1.2024) recommend universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma. (p. SBA-B)

The NCCN guidelines for an Occult Primary (1.2024) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology. (p. OCC-1)

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend MSI (among other studies) for patients with metastatic pancreatic cancer (p. PANC-1A) or resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12).

NCCN guidelines for Vulvar Cancer (3.2024) state to consider MSI testing for recurrent, progressive or metastatic squamous cell carcinoma of the vulva (p, VULVA-A, 2 of 4).

Tumor Specific *NPM1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (6.2023) 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

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Colon Cancer (1.2024) 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 (1.2024) 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 (1.2024) 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 (6.2023) 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 (1.2024) 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 (1.2024) 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 (3.2023) recommend baseline flow cytometric and/or molecular characterization of leukemic clone(s) 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 (2.2024) 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 (1.2024) 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 (1.2024), "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 (1.2024) 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 (1.2024) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. BINV-Q)

The NCCN guidelines for Biliary Tract Cancers (3.2023) 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 (1.2024) 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 (1.2024) recommend tumor analysis, including tumor mutational burden, for recurrent ovarian/Fallopian tube/primary peritoneal cancer. (p. OV-B 1 of 3)

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend testing tumor mutational burden for patients with resectable, borderline resectable, or locally advanced and metastatic pancreatic cancer as pembrolizumab may be considered for treatment. (p. PANC-F, 1 of 12, 6 of 12)

The NCCN guideline for Prostate Cancer (4.2023) 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 (1.2024) recommend consideration of tumor mutational burden testing for patients with endometrial cancer (p. ENDO-A 2 of

4). The guidelines also recommend tumor mutational burden testing be done for patients with uterine sarcoma. (p. UTSARC-A 1 of 8)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend tumor/somatic molecular profiling 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*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. (p. AMP-3)

NCCN guidelines for Bone Cancer (1.2024) state to consider testing for TMB and MMR/MSI to inform treatment options for metastatic chondrosarcoma, (p. CHON-4), metastatic chordoma (p. CHOR-3), widely metastatic Ewing sarcoma (p. EW-3), and metastatic osteosarcoma (p. OSTEO-3).

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (4.2023) states that several targeted therapeutic agents have been approved by the FDA for use in esophageal and EGJ cancers. Use of select immune checkpoint inhibitors is based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. (p. ESOPH-B, 5 of 6)

NCCN guidelines for Gastric Cancer (3.2023) indicate that next generation sequencing may be considered as part of the workup for gastric cancer (p. GAST-1). At present, several targeted therapeutic agents have been approved by the FDA for use in gastric cancer. Use of select immune checkpoint inhibitors is based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. (p. GAST-B, 5 of 6).

NCCN guidelines for Head and Neck Cancers (2.2024) indicates NGS profiling and other appropriate biomarker testing should be done to check the status of tumor mutational burden (TMB), among other biomarkers, prior to treatment for metastatic salivary gland tumors. (p. SALI-4)

NCCN guidelines for Neuroendocrine and Adrenal Tumors (1.2023) state that TMB testing should be considered for adrenocortical carcinoma (p. AGT-5), extra pulmonary poorly differentiated neuroendocrine carcinoma, large or small cell carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm (p. PDNEC-1A).

NCCN guidelines for Thyroid Carcinoma (4.2023) state that genomic testing to identify actionable mutations and tumor mutational burden (TMB) should be done for patients

with locally recurrent, advanced and/or metastatic papillary (p. PAP-10), follicular (p. FOLL-9) or oncocytic carcinoma (p. ONC-9) that is not amenable to RAI therapy, and for patients with stage IVC anaplastic carcinoma (p. ANAP-3).

NCCN guidelines for Vulvar Cancer (3.2024) indicate that tumor mutational burden (TMB) testing should be considered in the pathologic assessment for squamous cell carcinoma of the vulva (p. VULVA-A, 2 of 4).

NCCN guidelines for Small Bowel Adenocarcinoma (1.2024) recommend consideration of tumor mutational burden testing for metastatic adenocarcinoma (p. SBA-5).

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 April 2023) 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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