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 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 comprehensive 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

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies				
Solid Tumor-Type Agnostic Molecular Profiling Panel Tests	FoundationOne CDx (Foundation Medicine)	0037U	C00-D49, Z85	1, 2, 35
	MSK-IMPACT (Memorial Sloan Kettering Medical Center)	0048U		
	MI Cancer Seek - NGS Analysis (Caris Life Sciences)	0211U		
	Oncotype MAP™ PanCancer Tissue Test (OncotypeDX)	0244U		
	OmniSeq (Integrated Oncology)	81445, 81455		
	OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs)			
	Tempus xT (Tempus)			
	Precise Tumor Molecular Profiling (Myriad)			
	Guardant360 TissueNext (Guardant)	0334U		
Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81455	C91, C92, D46.9	9, 13, 15, 19
	NeoTYPE Myeloid Disorders Profile (NeoGenomics Laboratories)	81450		
	OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies (Mayo Clinic Laboratories)			
	Onkosight Myeloid Disorder Panel (BioReference Laboratories)			
	Tempus xT Hematologic Malignancy			
Tumor Agnostic Molecular Profiling	MI Cancer Seek - NGS Analysis (Caris Life Sciences	0211U	C00-D49, Z85	38

Panel Tests with IHC and Cytogenetic Analyses	MI Profile (Caris Life Sciences)	81445, 81455		
	OmniSeq (Integrated Oncology)			
	OnkoSight (GenPath)			
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)			
	SmartGenomics			
Colorectal Cancer Focused Molecular Profiling Panels	PraxisTM Extended RAS Panel (Illumina)	0111U	C18-C20	3, 4, 29
	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 Lung Comprehensive (BioReference Laboratories)	81445		
Cutaneous Melanoma Focused Molecular Profiling Panels	Melanoma Panel (Knight Diagnostics)	81210, 81404	C43, D03	12
	OnkoSight Melanoma Panel (BioReference Laboratories)	81445		
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML Gene Panel Assay (LabPMM, Invivoscribe Technologies)	0050U	C92, D47	13, 34
	NeoTYPE AML Prognostic Profile (NeoGenomics)	81450		
	LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)			
Myeloproliferative Neoplasms (MPNs) Panel	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories)	81219, 81270, 81339	D47	15, 16
	MPN, JAK2/MPL/CALR by NGS (BioReference Laboratories)	81219, 81270, 81279, 81338		
Single Gene Testing of Solid Tumors and Hematologic Malignancies				
Tumor Specific BCR/ABL (TKI Resistance) Kinase	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170	C92.1	19, 20, 21
	Onkosight NGS ABL1 Sequencing			

Domain Targeted Mutation Analysis	(BioReference Laboratories)			
Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis	BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics)	81206, 81207	C83, C85, C91, C92, D45, D47	13, 15, 19, 20, 21, 22, 34
	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 Targeted Mutation Analysis	BRAF Mutation Analysis (NeoGenomics)	81210	C18-C21, C34, C43, C71, C73, C91.4	1, 3, 7, 12, 17, 23, 24, 29
BRCA1/2 Variant Analysis	BRCA1 Mutation Analysis BRCA2 Mutation Analysis BRCA1/2 Mutation Analysis	81162, 81163, 81164, 81165, 81166, 81167, 81216	C56, C61	6, 8, 26, 30
Tumor Specific CALR Targeted Mutation Analysis	Calreticulin (CALR) Mutation Analysis (Quest Diagnostics)	81219	C94 D47.1	15
Tumor Specific CEBPA Sequencing	CEBPA Mutation Analysis (LabCorp)	81218	C92	13
EGFR Variant Analysis	EGFR Mutation Analysis (NeoGenomics Laboratories)	81235	C34	1, 7
FLT3 Variant Analysis	FLT3 ITD and TKD Mutation Detection (ARUP Laboratories)	81245, 81246	C92	9, 13, 20, 21, 34
	LeukoStrat CDx FLT3 Mutation Assay (Versiti)	0023U		
	FLT3 ITD MRD by NGS (LABPMM, Invivoscribe Technologies)	0046U		
Tumor Specific IDH1 and IDH2 Panel	IDH1 & IDH2 Mutation Analysis (NeoGenomics)	81120, 81121	C71, D49.6	24
Tumor Specific IGHV Somatic	IgVH Mutation Analysis (NeoGenomics)	81263	C83, C91	33

Hypermutation Analysis				
JAK2 Variant Analysis	JAK2 Exons 12 to 15 Sequencing (Mayo Clinic)	0027U	C91, C92, C94, D45, D47.1, D47.3, D75.81	9, 15, 20
	JAK2 Mutation (University of Iowa)	0017U		
	JAK2 V617F Mutation Analysis (Quest Diagnostics)	81270		
KIT Targeted Mutation Analysis	KIT Mutation Analysis (ProPath)	81272	C43, C49.A, C92, D47.1, D47.02	11, 12, 13, 14, 15, 34
	KIT (D816V) Digital PCR (Labcorp)	81273		
Tumor Specific KRAS Targeted Mutation Analysis	KRAS Mutation Analysis (NeoGenomics)	81275, 81276	C18-21, C34	1, 3, 7, 29
MGMT Methylation Analysis Tests	MGMT Promoter Methylation Assay (UCSF Molecular Diagnostics Laboratory)	81287	C71	24
Tumor Specific MLH1 Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics)	81288	C18-C21, C54.1	3, 4, 28
Tumor Specific MPL Targeted Mutation Analysis	MPL Mutation Analysis (MedFusion)	81338, 81339	D45, D47.1, D47.3, D75.81	15
Microsatellite Instability Analysis	Microsatellite Instability (MSI) by PCR (NeoGenomics)	81301	C15-C23, , C50, C53, C54.1, C62, C80,	3, 5, 10, 31, 32, 36, 37, 38, 39, 45
	Microsatellite Instability (MSI) Analysis (Ambry Genetics)			
Tumor Specific NPM1 Targeted Mutation Analysis	NPM1 MRD by NGS (LabPMM, Invivoscribe Technologies)	0049U	C92	13
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)	81310		
Tumor Specific NRAS Targeted Mutation Analysis	NRAS Mutation Analysis (NeoGenomics)	81311, 81304	C18-C21	3, 29
Tumor Specific PIK3CA Targeted	PIK3CA Mutation Analysis (Quest Diagnostics)	81309	C50, C55	5, 18

Mutation Analysis	PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp)	0155U, 0177U		
Tumor Specific RET Targeted Mutation Analysis	RET Targeted Mutation Analysis RET Sequencing Analysis	81404, 81405, 81406	C34, C73	7, 17
Tumor Specific TP53 Targeted Mutation Analysis	TP53 MutationAnalysis (NeoGenomics)	81352	C92, R71, R79	22, 33
Measurable (Minimal) Residual Disease (MRD) Analysis				
Measurable (Minimal) Residual Disease (MRD) Analysis	MyMRD® NGS Panel, Laboratory for Personalized Medicine	0171U	C91, R71, R79	20, 21, 33, 40
	ClonoSEQ (Adaptive Biotechnologies)	81479		
Tumor Mutational Burden (TMB)				
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479	C00-D49, Z85	50
	Tumor Mutational Burden (Nebraska Medical Center - Molecular Diagnostic Laboratory)			
Red Blood Cell Genotyping in Multiple Myeloma				
Red Blood Cell Genotyping in Multiple Myeloma	PreciseType HEA (Immucor)	0001U	C90.0, R71, R79	46, 47, 48
Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies				
Cancer Exome/Genome Sequencing	Oncomap ExTra (Exact Sciences Laboratories)	0329U	C00-D49, Z85	1, 50
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	81415, 81416, 81479		
	Tempus xE (Tempus)			
Genetic Testing to Confirm the Identity of Laboratory Specimens				
Genetic Testing to Confirm the Identity of Laboratory	know error® DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC)	81265, 81266, 81479	C00.0-D49	41, 42, 43, 44

Specimens	ToxProtect (Genotox Laboratories LTD)	0007U		

OTHER RELATED POLICIES

This policy document provides coverage criteria for *Oncology: 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 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

Solid Tumor-Type Agnostic Molecular Profiling Panel Tests

I. Molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0244U, 81445, 81455, 0334U) is considered **medically necessary** when:

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

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

II. Repeat molecular profiling panels for solid tumors is medically necessary when the member has progression of any of the following:

   A. Metastatic colon cancer, **OR**

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

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

   D. Metastatic prostate cancer, **OR**

   E. Ovarian cancer that is platinum-sensitive

III. Molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 81445, 81455) are considered **investigational** for all other indications.

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Comprehensive Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

I. Comprehensive molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) is 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 a newly diagnosed myelodysplastic syndrome with persistent cytopenia(s) (at least 4-6 months), **AND**

1. Other causes of cytopenia(s) have been ruled out, including:

a) Nutritional anemias (for example: iron deficiency anemia, folate deficiency anemia, vitamin B12 deficiency anemia), **AND**

b) Thyroid disease, **AND**

c) Drug-induced cytopenia, **AND**

d) Viral infection (for example: HIV), **OR**

C. The member is suspected to have a myeloproliferative neoplasm, **AND**

1. Comprehensive panel can be ordered as part of initial evaluation, or after *JAK2*, *CALR*, and *MPL* analysis were previously performed and the results were negative, **OR**

D. The member has a diagnosis of chronic myelogenous leukemia, **AND**

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

2. *BCR-ABL1* kinase domain mutation analysis has been performed and the results were negative.

II. Comprehensive 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. This COA is not intended to address liquid biopsies.

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Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses

I. Tumor Agnostic Molecular Profiling Panel Tests including or with IHC and Cytogenetic Analyses (0211U, 81445, 81455) are considered **medically necessary** when:

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

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

   C. One of the following:

      1. The member has not had previous comprehensive tumor molecular profiling or multi-technology molecular profiling for the primary cancer diagnosis, **OR**

      2. The member *HAS* had previous comprehensive tumor molecular profiling or multi-technology molecular profiling, and has a **new** primary cancer diagnosis for which this testing is being ordered.

II. Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses (0211U, 81445, 81455) are considered **investigational** for all other indications.

Colorectal Cancer Focused Molecular Profiling Panels

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

   A. The member has suspected or proven metastatic, synchronous or metachronous colorectal cancer, **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 diagnosis of colorectal cancer, **OR**

2. The member *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) is 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) is considered **medically necessary** when:

A. The member 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 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 has progression on targeted therapy for non-small cell lung cancer.

III. Lung cancer-focused molecular profiling panels (0022U, 81445) is 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 (81210, 81404, 81445) is 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 (81210, 81404, 81445) is 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) is 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) 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 (81219, 81270, 81279, 81338, 81339) 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), **AND**

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

II. Myeloproliferative neoplasm (MPN) molecular profiling panel (81219, 81270, 81279, 81338, 81339) analysis is considered **investigational** for all other indications.

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SINGLE-GENE TESTING OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

Tumor Specific BCR/ABL (TKI Resistance) Kinase Domain Targeted Mutation Analysis

I. Somatic *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. 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/ABL 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 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 workup for or to monitor disease progression 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* Targeted Mutation Analysis

I. Somatic *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, synchronous or metachronous 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 is being evaluated for:

1. Hairy cell leukemia (for individuals without cHCL immunophenotype).

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BRCA1/2 Variant Analysis

I. Somatic *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.

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Tumor Specific *CALR* Targeted Mutation Analysis

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

A. The member is suspected to have a myeloproliferative neoplasm.

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Tumor Specific *CEBPA* Sequencing Tests

I. Somatic *CEBPA* sequencing tests (81218) in hematologic malignancies is considered **medically necessary** when:

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

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EGFR Variant Analysis

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

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

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

3. Advanced or metastatic squamous cell lung carcinoma, **OR**
4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

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FLT3 Variant Analysis

I. Somatic *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 acute lymphocytic leukemia (ALL), **OR**,

C. The member has a diagnosis of myelodysplastic syndrome

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Tumor Specific *IDH1* and *IDH2* Panel

I. Somatic *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors is considered **medically necessary** when:

A. The member has a diagnosis of a glioma.

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Tumor Specific *IGHV* Somatic Hypermutation Analysis

I. Somatic *IGHV* variant analysis (81263) in hematologic malignancies is considered **medically necessary** when:

A. The member has a diagnosis of:

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

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JAK2 Variant Analysis

I. Somatic *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 (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).

B. The member has acute lymphoblastic leukemia

C. The member is suspected to have a myelodysplastic syndrome

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KIT Targeted Mutation Analysis Tests

I. Somatic *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 leukemia, **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* Targeted Mutation Analysis Tests

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

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

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

II. Somatic *KRAS* variant analysis (81275, 81276) in solid tumors, as a stand alone test, in an individual with non-small cell lung cancer (NSCLC) is considered **investigational**.

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MGMT Methylation Analysis Tests

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

   A. The member 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 Tests

I. Somatic *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**

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

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Tumor Specific *MPL* Targeted Mutation Analysis

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

   A. The member 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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Microsatellite Instability Analysis (MSI)

I. Somatic 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. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer, **OR**
5. Recurrent, progressive or metastatic cervical cancer, **OR**
6. Testicular cancer and has had 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. Metastatic and/or recurrent small bowel adenocarcinoma, **OR**
11. Metastatic occult primary.

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Tumor Specific *NPM1* Targeted Mutation Analysis

I. Somatic *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* Targeted Mutation Analysis

I. Somatic *NRAS* variant analysis (81311, 81304) in solid tumors is considered **medically necessary** when:

   A. The member has suspected or proven metastatic, synchronous or metachronous colorectal cancer.

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Tumor Specific *PIK3CA* Targeted Mutation Analysis

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

   A. The member has 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 *RET* Targeted Mutation Analysis

I. Somatic *RET* variant analysis (81404, 81405, 81406) in solid tumors is considered **medically necessary** when:

   A. The member has a diagnosis of medullary thyroid cancer, **OR**

   B. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma, **OR**

   C. Advanced or metastatic adenocarcinoma, large cell, or non small-cell cancer of the lung.

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Tumor Specific *TP53* Targeted Mutation Analysis

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

   A. The member has a diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL), **OR**

   B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL).

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Tumor Mutational Burden (TMB)

I. Tumor mutational burden testing (TMB) (81479) is considered **medically necessary** when member has any of the following:

   A. Recurrent or metastatic breast cancer, **OR**

   B. Recurrent, progressive or metastatic cervical cancer, **OR**

   C. Unresectable or metastatic gallbladder cancer, **OR**

   D. Unresectable or metastatic extrahepatic cholangiocarcinoma, **OR**

   E. Suspected metastatic malignant occur primary tumor, **OR**

   F. Recurrent ovarian/fallopian tube/primary peritoneal cancer, **OR**

   G. Metastatic or advanced pancreatic adenocarcinoma, **OR**

   H. Metastatic castration-resistant prostate cancer, **OR**

   I. Progression of testicular cancer after high dose or third line therapy, **OR**

   J. Endometrial carcinoma or uterine sarcoma

MEASURABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS

I. Measurable (minimal) residual disease analysis (0171U, 81479) in bone marrow or peripheral blood is **medically necessary** when:

   A. The member has a diagnosis of:

      1. Acute Lymphocytic Leukemia (ALL), **OR**

      2. Multiple Myeloma, **OR**

      3. Chronic Lymphocytic Leukemia

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RED BLOOD CELL GENOTYPING IN MULTIPLE MYELOMA

I. Red blood cell genotyping (0001U) 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 with Daratumumab (DARA), **AND**

   C. One of the following:

      1. Auto- or allo-antibodies are detected, **OR**

      2. RBC phenotyping cannot be performed due to a transfusion within the prior three months.

CANCER EXOME/GENOME SEQUENCING

I. Whole exome sequencing and whole genome sequencing in solid tumors (0329U, 81415, 81416, 81479) and hematologic malignancies (0329U, 81425, 81426, 81479) 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, ToxProtect, ToxLok) (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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Medically Necessary Tumor Testing By Cancer Type:

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Any solid tumor	Comprehensive molecular profiling panel for solid tumors	Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer
ALL	BCR-ABL1, TCF3-PBX1, ETV6-RUNX1, IL3-IGH, KMT2A, ABL2, CRLF2, CSF1R, EPOR, FLT3, IL7R, JAK1, JAK2, JAK3, PDGFRB, SH2B3, MRD	At diagnosis, or relapsed/refractory disease
AML	FISH, karyotype rearrangements: CBFB-MYH11, GAT2-MECOM, BCR-ABL, KMT2A-MLLT3, DEK-NUP214, RUNX1, RUNX1T1, ASXL1, KIT, NPM1, RUNX1, TP53, CEBPA, FLT3, IDH1, IDH2, Comprehensive-molecular profiling panel	Workup
Ewing Sarcoma (bone cancer)	Translocations: ETV1, ETV4, EWSR1, FEV, FLI1, ERG, FUS,	Initial workup
Ewing Sarcoma (bone cancer)	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Progression after treatment
Breast Cancer	BRCA1, BRCA2, PD-L1, PIK3CA, NTRK1/2/3, MSI, MLH1, MSH2, MSH6, PMS2, TMB	Recurrent or metastatic
CNS Cancer Glioma-low grade	1p/19q, TERT promoter, H3F3A, HIST1H3B, BRAF, IDH1, IDH2, ATRX, MGMT Promoter Methylation	Pre-adjuvant therapy
CNS Cancer Medulloblastoma	APC, CTNNB1, GAB1, YAP1, TP53	Post-operative staging
Cervical Cancer	MLH1, MSH2, MSH6, PMS2, MSI, PD-L1, NTRK1/2/3, TMB,	Recurrent, progressive or metastatic disease
CLL/SLL	CCND1, 11:14 translocation, 11q:v translocation, CD19, CD200, CD5, FCER2, IGK, IGL, MME, MS4A1, CD247, CD3D, CD3E, CD3G, LEF1, ATM, CD38, IGH, ITGA4, ZAP70, TP53	Initial diagnosis
CML	BCR-ABL1, ABL1 Kinase Domain	Chronic phase adult CML

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Colorectal Cancer	BRAF, KRAS, NRAS, HER2 amplifications (by NGS or IHC) MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC) if not previously done NTRK1/2/3, Comprehensive molecular profiling panel	Invasive, metastatic, synchronous (any T, any N, M1)
Colorectal Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Newly diagnosed
Cutaneous Melanoma	BRAF, KIT	Workup for metastatic or recurrent disease
Esophageal and EGJ Cancers	HER2, PD-L1, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Locally advanced, recurrent or metastatic adenocarcinoma
Gallbladder Cancer	MSI or MMR (MLH1, MSH2, MSH6 PMS2 by IHC) BRAF, ERBB2, FGFR2, IDH1, NTRK1/2/3, TMB	Unresectable or metastatic disease
Gastric Cancer	HER2, PD-L1, MSI if not previously done, NTRK1/2/3, Comprehensive molecular profiling panel	Locally advanced, recurrent or metastatic disease
Gastric Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Workup
Hairy Cell Leukemia	CCND1, CD19, CD200, CD22, CD5, IL2RA, IL3RA, ITGAE, ITGAX, MME, MS4A21, BRAF, IGH	Initial diagnosis
Hepatobiliary Cancers	MSI (PCR) or MMR (MLH1, MSH2, MSH6, PMS2 by IHC) TMB, BRAF, HER2, FGFR2, IDH1, NTRK1/2/3, RET	Unresectable or metastatic extrahepatic cholangiocarcinoma
Mantle Cell Lymphoma	TP53, CD19, CD5, FCER2, IGK, IGL, MME, MS4A1, BCL2, BCL6, CCND1, CD3E, CR2, MKI67, SOX11, IGH, CCND2 rearrangement, CCND3 rearrangement, CCND1	Initial diagnosis
Multiple Myeloma	MRD	Follow up/surveillance

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Myelodysplastic Syndrome	ASXL1, BCOR, CALR, CBL, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2 Comprehensive hematologic malignancy panel testing	Initial evaluation
Myeloproliferative Neoplasms (polycythemia vera PV, essential thrombocythemia ET, myelofibrosis MF)	BCR-ABL, cytogenetics, FISH, Comprehensive molecular profiling panel For PV, ET, MF: JAK2, For ET, MF: MPL, CALR, ASXL1, EZH2, RAS	Diagnosis and prognostication
Non-small Cell Lung Cancer	EGFR, KRAS, MET, NTRK1/2/3, RET, ALK, ROS1, BRAF, PD-L1 (IHC), Comprehensive molecular profiling panel	Pre-adjuvant therapy, metastatic disease
B-Cell Lymphomas	IGH, IGK, IGL	Initial diagnosis
Occult Primary	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB, Comprehensive molecular profiling panel	Initial evaluation of suspected malignancy
Ovarian Cancer	BRCA1/2, homologous recombination deficiency, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), Comprehensive molecular profiling panel	Recurrent disease (if not previously done)
Pancreatic Adenocarcinoma	ALK, BRAF, BRCA1, BRCA2, ERBB2, FGFR2, KRAS, MLH1, MSH2, MSH6, NRG1, NTRK1, NTRK2, NTRK3, PALB2, PMS2, RET, ROS1 MSI and/or MMR (MLH1, MSH2, MSH6, PMS2)	Locally advanced or metastatic disease
Prostate Cancer	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L,	Metastatic disease

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Prostate Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB	Progressive metastatic disease
Testicular Cancer	MSI, MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB	Recurrent disease
Thyroid Carcinoma (anaplastic carcinoma)	BRAF, ALK, RET, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2)	Initial workup
Thyroid Carcinoma (anaplastic, follicular, Hürthle cell, medullary, papillary carcinomas)	BRAF, ALK, RET, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2)	Recurrence or metastatic disease
Uterine Neoplasms (endometrial carcinoma)	MMR (MLH1, MSH2, MSH6, PMS2 by IHC) TMB, NTRK1/2/3, POLE, TP53 expression Comprehensive genomic profiling panel	Diagnosis
Uterine Neoplasms (uterine sarcoma)	NTRK1/2/3, TMB, MSI	Metastatic or recurrent disease

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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)

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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

Solid Tumor-Type Agnostic Molecular Profiling Panel Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on occult primary (1.2022) 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 in individuals with localized adenocarcinoma or carcinoma not otherwise specified.

The NCCN guideline on non-small cell lung cancer (3.2022) 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 NCCN guideline for colon cancer (1.2022) 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).

The NCCN guideline for gastric cancer (2.2022) recommends that patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering trastuzumab therapy have IHC for *HER2* and NGS when limited diagnostic tissue is available or patient can't undergo a traditional biopsy. (p. GAST-B 3 of 6).

The NCCN guideline for ovarian cancer (1.2022) 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)

The NCCN guideline for pancreatic adenocarcinoma (1.2022) 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 (3.2022) 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. They also recommend Tumor testing for alterations in homologous recombination DNA report genes such as *BRCA1/2, ATM, PALB2, FANCA, RAD512D, CHECK2, CDK12*, is for patients with metastatic prostate cancer. (p. PROS-B)

American Society of Clinical Oncology (ASCO)

The American Society of Clinical Oncology (2018) endorsed the College of American Pathologists/International Association for the Study of Lung cancer/Association of Molecular Pathology Clinical Practice Guideline Update for Molecular Testing for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors which recommends that physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection. They further recommend that multiplexed genetic sequencing panels are preferred where available over multiple single gene tests to identify other treatment options beyond *EGFR, ALK, BRAF,* and *ROS1*.

The panel recommends that *EGFR, ALK, ROS1* and *BRAF* testing should be performed on all patients with advanced lung adenocarcinoma. They went on to state that *RET, HER2, KRAS,* and *MET* molecular testing are not indicated as stand alone tests but are appropriate to include as part of a larger testing panel

US Food and Drug Administration (FDA)

On November 30, 2017, FoundationOne CDx (Foundation Medicine, Inc.) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as a companion diagnostic to identify patients who may benefit from treatment with a defined set of targeted therapies in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms.

On November 15, 2017, MSK-IMPACT (Memorial Sloan Kettering) was approved by the U.S Food and Drug Administration (FDA) through the premarket approval process. The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next

generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for acute myeloid leukemia (2.2022) 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 myelodysplastic syndromes (3.2022) recommend that 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. MS-3) NCCN describes cytopenia that is suspicious for myelodysplasia as the presence of peripheral blood dysplasia, blasts, or MDS-associated cytogenetic abnormalities. They say cytopenias are defined as values lower than standard lab hematologic levels, being cognizant of age, sex, ethnic, and altitude norms (p. MDS-1, p. MDS-2). NCCN recommends ruling out other causes of anemia, such as nutritional deficiency of folate and vitamin B12, as well as measuring thyroid stimulating hormone levels, and HIV testing if clinically indicated (p. MDS-1).

The NCCN guidelines for myeloproliferative neoplasms (2.2022) 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 (3.2022) 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).

Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses

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Colorectal Cancer Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for colon cancer (1.2022) 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 (3.2022) recommends that at this time when feasible, testing be performed via a broad, panel-based approach for individuals with non-small cell lung cancer. For patients who do not have identifiable driver oncogenes via the broad panel-based approach, RNA-based NGS should be considered in order to detect clinically significant fusion events.

Cutaneous Melanoma Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for cutaneous melanoma (3.2022) 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 (2.2022) 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).

Myeloproliferative Neoplasms (MPNs) Panel

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on myeloproliferative neoplasms (2.2022) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts is recommended to exclude the diagnosis of CML. 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.

Tumor Specific BCR/ABL (TKI Resistance) Kinase Domain Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on chronic myeloid leukemia (3.2022) 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. Guidelines for discontinuation of tyrosine kinase inhibitor therapy are detailed.

Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on pediatric acute lymphocytic leukemia (1.2022) 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.

The NCCN guidelines on acute lymphocytic leukemia (1.2022) 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.

The NCCN guidelines on B-cell lymphoma (3.2022) include molecular testing for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphocytic leukemia.

American Society of Clinical Oncology (ASCO)

ASCO (2018) endorsed the College of American Pathologists and American Society of Hematology Guideline with the following relevant guidelines for the initial workup for acute leukemia:

- **Recommendation 5**. In addition to performing morphologic assessment (blood and BM), the pathologist or treating clinician should obtain sufficient samples and

perform conventional cytogenetic analysis (ie, karyotype), appropriate molecular genetic and/or FISH testing, and FCI. The flow cytometry panel should be sufficient to distinguish AML (including APL), including early T-ALL, B-ALL, and AL of ambiguous lineage in all patients diagnosed with AL. Molecular genetic and/or FISH testing does not, however, replace conventional cytogenetic analysis (Strong recommendation).

- **Recommendation 12**. For patients with suspected or confirmed AL, the pathologist or treating clinician should ensure that flow cytometry analysis or molecular characterization is comprehensive enough to allow subsequent detection of MRD (Strong recommendation).
- **Recommendation 13**. For pediatric patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(12;21)(p13.2;q22.1); ETV6-RUNX1, t(9;22)(q34.1;q11.2); *BCR-ABL1, KMT2A* (MLL) translocation, iAMP21, and trisomy 4 and 10 is performed (Strong recommendation).
- **Recommendation 14**. For adult patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1* is performed. In addition, testing for *KMT2A* (*MLL*) translocations may be performed. (Strong recommendation for testing for t(9;22)(q34.1;q11.2) and *BCR-ABL1*; Recommendation for testing for *KMT2A* (*MLL)* translocations).
- **Recommendation 15**. For patients with suspected or confirmed ALL, the pathologist or treating clinician may order appropriate mutational analysis for selected genes that influence diagnosis, prognosis, and/or therapeutic management, which include, but are not limited to, *PAX5, JAK1, JAK2*, and/or *IKZF1* for B-ALL and *NOTCH1* and/or *FBXW7* for T-ALL. Testing for overexpression of *CRLF2* may also be performed for B-ALL (Recommendation).
- **Recommendation 16**. For pediatric and adult patients with suspected or confirmed AML of any type, the pathologist or treating clinician should ensure that testing for *FLT3-ITD* is performed. The pathologist or treating clinician may order mutational analysis that includes, but is not limited to, *IDH1, IDH2, TET2, WT1, DNMT3A*, and/or *TP53* for prognostic and/or therapeutic purposes. (Strong recommendation for testing for *FLT3-ITD*; Recommendation for testing for other mutational analysis).
- **Recommendation 17**. For adult patients with confirmed core binding factor (CBF) AML (AML with t(8;21)(q22; q22.1); *RUNX1-RUNX1T1* or inv(16)(p13.1q22)/t(16;16)(p13.1;q22); *CBFB-MYH11*), the pathologist or treating clinician should ensure that appropriate mutational analysis for *KIT* is performed. For pediatric patients with confirmed CBF AML; *RUNX1-RUNX1T1* or inv(16)(p13.1q22)/t(16;16)(p13.1;q22); *CBFB-MYH11*, the pathologist or treating

clinician may ensure that appropriate mutational analysis for *KIT* is performed. (Strong recommendation for testing for *KIT* mutation in adult patients with CBF AML; Expert consensus opinion for testing for *KIT* mutation in pediatric patients with CBF AML).

- **Recommendation 18**. For patients with suspected APL, the pathologist or treating physician should also ensure that rapid detection of *PML-RARA* is performed. The treating physician should also order appropriate coagulation studies to evaluate for disseminated intravascular coagulation (Strong recommendation).

Tumor Specific BRAF Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on thyroid carcinoma (2.2022) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS and somatic *RET* testing in all individuals with newly diagnosed medullary thyroid carcinoma. 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.

The NCCN guideline on hairy cell leukemia (1.2022) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL Immunophenotype.

The NCCN guideline on cutaneous melanoma (3.2022) 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.

The NCCN guideline on central nervous system cancers (2.2021) states that *BRAF* fusion and/or mutation testing is clinically indicated in patients with low-grade glioma or pilocytic astrocytoma and that *MGMT* promoter methylation analysis is an essential part

of work-up for all high grade gliomas (grade III and IV). The panel also recommends *IDH* mutation testing in patients with glioma.

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
- 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.

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
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification
- *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

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

BRCA1/2 Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer (1.2022) 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. 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.

The NCCN guideline on prostate cancer (3.2022) 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.

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.

- 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.
- Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer.
- 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.
- Clinical decision making should not be made based on a variant of uncertain significance.
- Women with epithelial ovarian cancer should have testing at the time of diagnosis.

Tumor Specific CALR Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on myeloproliferative neoplasms (2.2022) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts is recommended to exclude the diagnosis of CML. 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.

Tumor Specific CEBPA Sequencing

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (1.2022) 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.

FLT3 Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (1.2022) 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.

Tumor Specific IDH1 and IDH2 Panel

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (1.2022) 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.

The NCCN guideline on central nervous system cancers (2.2021) states that *BRAF* fusion and/or mutation testing is clinically indicated in patients with low-grade glioma or pilocytic astrocytoma and that *MGMT* promoter methylation analysis is an essential part of work-up for all high grade gliomas (grade III and IV). The panel also recommends *IDH* mutation testing in patients with glioma.

JAK2 Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on myeloproliferative neoplasms (2.2022) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts to exclude the diagnosis of CML. Additionally, they 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.

KIT Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on cutaneous melanoma (3.2022) 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.

Current NCCN guidelines for gastrointestinal stromal tumors (1.2022) recommend *KIT* mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor.

Tumor Specific KRAS Targeted Mutation

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
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification
- *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
- 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
- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors

MGMT Methylation Analysis Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on central nervous system cancers (2.2021) states that *BRAF* fusion and/or mutation testing is clinically indicated in patients with low-grade glioma or pilocytic astrocytoma and that *MGMT* promoter methylation analysis is an essential part of work-up for all high grade gliomas (grade III and IV). The panel also recommends *IDH* mutation testing in patients with glioma.

Tumor Specific MLH1 Methylation Analysis

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

- 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.

Microsatellite Instability Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for colon cancer (1.2022) recommend determination of tumor MMR and MSI in all individuals with colorectal cancer. Additionally, they recommend determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplification individually or as part of an NGS panel in all individuals with suspected or proven metastatic, synchronous or metachronous colorectal cancer.

The NCCN guideline on gastric cancer (2.2022) recommends MSI and MMR testing should be performed for all newly diagnosed gastric cancers. Additionally, the guideline recommends *PD-L1* and *HER2* testing if metastatic disease is documented/suspected.

The NCCN guideline on esophageal and esophagogastric junction cancer (1.2021) recommends MSI by PCR, MMR by IHC, *PD-L1* and *HER2* testing if metastatic disease is documented/suspected.

The NCCN guideline for testicular cancer (1.2021) recommends MSI testing in individuals with testicular cancer who have had progression after high-dose chemotherapy or third line therapy.

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
- 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.

Tumor Specific NPM1 Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (1.2022) 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.

Tumor Specific NRAS Targeted Mutation 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
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification
- *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
- 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
- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors

Tumor Specific PIK3CA Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on breast cancer (3.2022) 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.

Tumor Specific RET Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on thyroid carcinoma (2.2022) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS and somatic *RET* testing in all individuals with newly diagnosed medullary thyroid carcinoma. 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.

Tumor Specific TP53 Targeted Mutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (1.2022) 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.

The NCCN guidelines on B-cell lymphoma (3.2022) 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.

The NCCN guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (1.2022) 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. Minimal residual disease testing at the end of treatment for CLL is recommended.

Measurable (Minimal) Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for acute lymphoblastic leukemia (1.2022) 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 (1.2022) recommend consideration of MRD testing by NGS in the initial diagnostic workup (p. MYEL-1), follow up/surveillance (p. MYEL-4), prognostication (p. MYEL-5).

The NCCN guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (1.2022) 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).

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