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				
Comprehensive Molecular Profiling Panels for Solid Tumors	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	0244U		
	MI Profile (Caris Life Sciences)	81445, 81455		
	OmniSeq (Integrated Oncology)			
	OnkoSight (GenPath)			
	Tempusl xT (Tempus)			
	SmartGenomics			
Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81455	C91, C92	9, 13, 15, 16, 19, 34
	NeoTYPE Myeloid Disorders Profile (NeoGenomics Laboratories)	81450		
	OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies (Mayo Medical Laboratories)			
	Onkosight Myeloid Disorder Panel (BioReferences Laboratories)			
Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic	MI Cancer Seek - NGS Analysis (Caris Life Sciences	0211U	C00-D49, Z85	1, 2, 35
	MI Profile (Caris Life Sciences)	81445, 81455		

Analyses	OmniSeq (Integrated Oncology)			
	OnkoSight (GenPath)			
	Tempus xT (Tempus)			
	SmartGenomics			
Colorectal Cancer Focused Molecular Profiling Panels	PraxisTM Extended RAS Panel (Illumina)	0111U	C18-C20	3, 4, 29
	SmartGenomics NGS Colon (PathGroup)	81301, 81445		
	Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)			
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test (Thermo Fisher)	0022U	C34	1, 7
	Lung Cancer Panel (ARUP Laboratories)	81445		
	OnkoSight Lung Comprehensive (Bioreference Laboratories)			
Cutaneous Melanoma Focused Molecular Profiling Panels	Melanoma Panel (Knight Diagnostics)	81210, 81273, 81311, 81403, 81404, 81445, 88363	C43, D03	12
	OnkoSight Melanoma Panel (Bioreference Laboratories)			
	Symgene Focus - NGS Melanoma (CellNetix Pathology and Laboratory)			
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML NGS Panel (LabPMM, Invivoscribe Technologies)	0050U	C92, D47	13, 34
	Legacy AML Molecular Profile (NeoGenomics)	81450		
	LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)			
Myeloproliferative Neoplasms (MPNs) Focused Molecular Profiling Panel	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories)	81206, 81207, 81208, 81270, 81219, 81402, 81403	C91, C92, D45, D47	9, 16
	MPN, JAK2/MPL/CALR by NGS (BioReferences Laboratories)			

Single Gene Testing of Solid Tumors and Hematologic Malignancies				
ABL1 Kinase Domain Analysis	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170	C92.1	19, 20, 21
BCR/ABL Breakpoint Analysis	BCR/ABL1 Quantitative Analysis, BCR/ABL1 Qualitative Analysis, BCR/ABL1 P190 Quantitation, BCR/ABL1 P210 Quantitation	81206, 81207, 81208	C83, C85, C91, C92, D45, D46	13, 15, 19, 20, 21, 22, 34
	BCR-ABL1 major and minor breakpoint fusion transcripts (University of Iowa)	0016U		
	MRDx BCR-ABL Test (MolecularMD)	0040U		
BRAF Variant Analysis	BRAF V600E Targeted Mutation Analysis	81210	C18-C20, C24, 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
CALR Variant Analysis	CALR Sequencing Analysis	81219	C91, C92, C94, D45, D47.1, D47.3, D75.81	15
CEBPA Variant Analysis	CEBPA Targeted Mutation Analysis	81218	C92	12, 13
EGFR Variant Analysis	EGFR Targeted Mutation Analysis	81235	C34	1, 7
FLT3 Variant Analysis	FLT3 ITD Variant Analysis FLT3 TKD Variant Analysis	81245, 81246	C92	9, 15, 20, 21, 34
	LeukoStrat CDx FLT3 Mutation Assay (LabPMM, Invivoscribe Technologies)	0023U		
	FLT3 ITD MRD by NGS (LABPMM, Invivoscribe Technologies)	0046U		
IDH1 and IDH2 Variant Analysis	IDH1 Variant Analysis IDH2 Variant Analysis	81120, 81121	C71, D49.6	24

IGHV Variant Analysis	IGHV Variant Analysis	81261, 81262, 81263	C83, C91	33
JAK2 Variant Analysis	JAK2 Exons 12 to 15 Sequencing (Mayo Clinic)	0027U	C91, C92, C94, D45, D47.1, D47.3, D75.81	15
	JAK2 Mutation (University of Iowa)	0017U		
	JAK2 Targeted Mutation Analysis	81270		
KIT Variant Analysis	KIT Targeted Mutation Analysis	81272, 81273	C43, C49, D47.02	11, 12, 13, 14, 15, 34
KRAS Variant Analysis	KRAS Targeted Mutation Analysis	81275, 81276, S3713	C18-20	3, 7, 18, 29
MGMT Promoter Methylation Analysis	MGMT Methylation Analysis	81287	C71	24
MLH1 Promoter Methylation Analysis	MLH1 Methylation Analysis	81288	C18-C20, C54.1	3, 4, 28
MPL Variant Analysis	MPL Targeted Mutation Analysis	81402, 81403	C91, C92, C94, D45, D47.1, D47.3, D75.81	15
Microsatellite Instability Analysis	Microsatellite Instability Analysis	81301	C15, C17-C20, C25, C54.1, D44.10-D44.12	3, 5, 10, 31, 32, 36, 37, 38, 39, 45
NPM1 Variant Analysis	NPM1 MRD by NGS (LabPMM, Invivoscribe Technologies)	0049U	C92.20-C92.22	13
	NPM1 Targeted Mutation Analysis	81310		
NRAS Variant Analysis	NRAS Targeted Mutation Analysis	81311	C18-C20	3, 29
PIK3CA Variant Analysis	PIK3CA Targeted Mutation Analysis	81309	C50, C55	5, 18

	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	0155U, 0177U		
RET Variant Analysis	RET Targeted Mutation Analysis RET Sequencing Analysis	81404, 81405, 81406	C34, C73	7, 17
TP53 Variant Analysis	TP53 Sequencing Analysis	81405	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		
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
	Navigator ABO Sequencing (Grifols Immunohematology Center)	0180U		
	Navigator ABO Blood Group NGS (Grifols Immunohematology Center)	0221U		
Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies				
Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	MatePair Targeted Rearrangements, Oncology (Mayo Medical Laboratories)	0013U	C00-D49, Z85	1, 50
	MatePair Targeted Rearrangements, Hematologic (Mayo Medical Laboratories)	0014U		
	MatePair Acute Myeloid Leukemia Panel (Mayo Medical Laboratories)	0056U		
	EXaCT-1 Whole Exome Testing (Weill Cornell Medicine)	0036U		
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	81415, 81416		
	GPS Cancer (NantHealth)			
	Tempus xE (Tempus)			
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-C80.2	41, 42, 43, 44
	ToxProtect (Genotox Laboratories LTD)	0007U		
	ToxLok™ (InSource Diagnostics)	0079U		

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.

back to top

COVERAGE CRITERIA

MOLECULAR PROFILING PANEL TESTING OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

Comprehensive Molecular Profiling Panels for Solid Tumors

I. Comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0244U, 81445, 81455) 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), **AND**

   C. One of the following:

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

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

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

back to top

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 a suspected or confirmed diagnosis of acute myeloid leukemia (AML), **OR**

B. The member has persistent cytopenia(s) (at least 4-6 months) and a myelodysplastic syndrome is suspected or has been newly diagnosed, **AND**

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

a) Nutritional anemias (e.g., iron deficiency anemia, folate deficiency anemia, vitamin B12 deficiency anemia), **AND**

b) Thyroid disease, **AND**

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

d) Viral infection (e.g., HIV), **OR**

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

1. JAK2, CALR, MPN, and BCR/ABL analysis were previously performed and the results were negative, **AND**

2. Clinical suspicion for a myeloid neoplasm remains high, **OR**

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

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

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.

back to top

Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses

I. Tumor Agnostic Molecular Profiling Panel Tests 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 (e.g., 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, 81301, 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, 81301, 81445) is considered **investigational** for all other indications.

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

back to top

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), **AND**

C. One of the following:

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

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

II. Lung cancer-focused molecular profiling panels (81445, 0022U) is considered **investigational** for all other indications.

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

back to top

Cutaneous Melanoma Focused Molecular Profiling Panels

I. Cutaneous melanoma focused molecular profiling panels (81210, 81273, 81311, 81403, 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, 81273, 81311, 81403, 81404, 81445) is considered **investigational** for all other indications.

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

back to top

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

I. Acute myeloid leukemia focused molecular profiling panels (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 (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.

back to top

Myeloproliferative Neoplasms (MPNs) Molecular Profiling Panel

I. Myeloproliferative neoplasm (MPN) molecular profiling panel (81206, 81207, 81208, 81270, 81219, 81402, 81403) 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 (81206, 81207, 81208, 81270, 81219, 81402, 81403) analysis is considered **investigational** for all other indications.

back to top

SINGLE-GENE TESTING OF SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

ABL1 Kinase Domain 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.

back to top

BCR/ABL1 Breakpoint Analysis

I. Somatic *BCR/ABL1* breakpoint analysis (0016U, 0040U, 81206, 81207, 81208) 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 lymphocytic leukemia (ALL), **OR**
      2. Acute myeloid leukemia (AML), **OR**

3. Chronic myelogenous leukemia (CML), **OR**
4. Lymphocytic leukemia.

back to top

BRAF Variant 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. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma, **OR**
5. Low-grade glioma or pilocytic astrocytoma, **OR**

B. The member is being evaluated for:

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

back to top

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.

back to top

CALR Variant Analysis

I. Somatic *CALR* variant analysis (81219) in solid tumors or 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).

back to top

CEBPA Variant Analysis

I. Somatic *CEBPA* variant analysis (81218) in solid tumors or hematologic malignancies is considered **medically necessary** when:

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

back to top

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).

back to top

FLT3 Variant Analysis

I. Somatic *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in solid tumors or 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), **AND**

      1. Previous testing for BCR-ABL1 was negative.

back to top

IDH1 and *IDH2* Variant Analysis

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.

back to top

IGHV Variant Analysis

I. Somatic *IGHV* variant 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 small lymphocytic leukemia (SLL), **OR**

2. Primary cutaneous B-cell lymphoma, **OR**
3. Mantle cell lymphoma, **OR**
4. Post-transplant lymphoproliferative disorder.

back to top

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 amyeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).

back to top

KIT Variant Analysis

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 worked up 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).

back to top

KRAS Variant Analysis

I. Somatic *KRAS* variant analysis (81275, 81276, S3713) in solid tumors is considered **medically necessary** when:

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

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

II. Somatic *KRAS* variant analysis (81275, 81276, S3713) in solid tumors, as a stand alone test, in an individual with non-small cell lung cancer (NSCLC) is considered **investigational**.

back to top

MGMT Promoter Methylation Analysis

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 oligoastrocytoma, **OR**
      3. Anaplastic astrocytoma, **OR**
      4. Anaplastic glioma, **OR**
      5. Glioblastoma.

back to top

MLH1 Promoter Methylation Analysis

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.

back to top

MPL Variant Analysis

I. Somatic *MPL* variant analysis (81402, 81403) in or 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.

back to top

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. Locally advanced or metastatic pancreatic adenocarcinoma, **OR**
      4. Gastric cancer, **OR**

5. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer, **OR**
6. Recurrent, progressive or metastatic cervical cancer, **OR**
7. Testicular cancer and has had progression after high dose chemotherapy or third-line therapy, **OR**
8. Unresectable or metastatic Ewing's sarcoma, **OR**
9. Unresectable or metastatic gallbladder cancer, **OR**
10. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma, **OR**
11. Unresectable or metastatic breast cancer, **OR**
12. Metastatic and/or recurrent small bowel adenocarcinoma, **OR**
13. Metastatic occult primary.

back to top

NPM1 Variant 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).

back to top

NRAS Variant Analysis

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

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

back to top

PIK3CA Variant 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 carcinosarcoma or uterine rhabdomyosarcoma.

back to top

RET Variant 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.

back to top

TP53 Variant Analysis

I. Somatic ***TP53*** variant analysis (81405) 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).

back to top

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

back to top

RED BLOOD CELL GENOTYPING IN MULTIPLE MYELOMA

I. Red blood cell genotyping (81479, 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 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.

WHOLE EXOME AND WHOLE GENOME SEQUENCING IN CANCER

I. Whole exome sequencing and whole genome sequencing in solid tumors (0013U, 0036U, 81415, 81416) and hematologic malignancies (0014U, 0056U, 81425, 81426) is considered **investigational**.

back to top

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, 0079U, 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.

back to top

Medically Necessary Tumor Testing By Cancer Type:

Cancer Type	**Molecular Analysis** (see coverage criteria sections above)
Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer	Comprehensive molecular profiling panel for solid tumors
ALL	BCR/ABL1, FLT3, KIT, cytogenetics (link to policy), MRD
AML	CEBPA, FLT3, KIT, Targeted panel testing, Comprehensive hematologic malignancy panel testing
Ewing Sarcoma	MSI
Breast Cancer	PIK3CA, MSI
CNS Cancer	MGMT Promoter Methylation, IDH1/IDH2
Cervical Cancer	MSI
CLL/SLL	IGHv, TP53
CML	BCR/ABL1, ABL1 Kinase Domain
Colorectal Cancer	BRAF, KRAS, NRAS, MSI, Targeted panel testing

Cutaneous Melanoma	BRAF, KIT
Esophageal and EGJ Cancers	MSI
Gallbladder Cancer	MSI
Gastric Cancer	MSI
Hairy Cell Leukemia	BRAF
Hepatobiliary Cancers	MSI
Mantle Cell Lymphoma	IGHv
Multiple Myeloma	MRD
Myelodysplastic Syndrome	Targeted panel testing, Comprehensive hematologic malignancy panel testing
Myeloproliferative Neoplasms	JAK2, MPL, CALR, Targeted panel testing
Non-small Cell Lung Cancer	EGFR, Targeted panel testing, Comprehensive panel testing
B-Cell Lymphomas	IGHv
Occult Primary	MSI
Ovarian Cancer	BRCA1/2
Pancreatic Adenocarcinoma	MSI
Prostate Cancer	BRCA1/2
Testicular Cancer	MSI
Thyroid Carcinoma	BRAF, NTRK, ALK, RET
Uterine Neoplasms	KRAS, MLH1 Promoter Methylation, PIK3CA

back to top

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. **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)

back to top

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.

back to top

NOTES AND DEFINITIONS

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.

BACKGROUND AND RATIONALE

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN):

Colon Cancer

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Colorectal Cancer (v1.2021) state that abnormal MLH1 IHC should be followed by either germline genetic testing or tumor testing for MLH1 methylation for colorectal or endometrial cancers.

The NCCN guidelines on Oncology: Colon Cancer (v2.2021) 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.

Lung Cancer

The NCCN (v3.2021) 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.

Breast Cancer

The NCCN guidelines on Oncology: Breast Cancer (v8.2021) 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.

Thyroid Carcinoma

The NCCN (v2.2021) guidelines on thyroid carcinoma 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.

Acute Myeloid Leukemia

The NCCN guidelines on acute myeloid leukemia (v2.2021) 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.

Myelodysplastic Syndromes

The NCCN guidelines on myelodysplastic syndromes (v3.2021) state that genetic testing for somatic mutations in genes associated with MDS using gene panels is highly recommended.

Myeloproliferative Neoplasms

The NCCN guidelines on myeloproliferative neoplasms (v2.2021) 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.

Chronic Myelogenous Leukemia

The NCCN guidelines on chronic myelogenous leukemia (v1.2022) 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.

Pediatric Acute Lymphocytic Leukemia

The NCCN guidelines on pediatric acute lymphocytic leukemia (v2.2021) 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.

Acute Lymphocytic Leukemia

The NCCN guidelines on acute lymphocytic leukemia (v2.2021) 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.

B-Cell Lymphomas

The NCCN guidelines on B-cell lymphoma (v2.2021) include molecular testing for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphocytic leukemia.

The NCCN guidelines on B-cell lymphoma (v2.2021) 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.

Hairy Cell Leukemia

The NCCN guideline on Hairy Cell Leukemia (v1.2022) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL Immunophenotype.

Cutaneous Melanoma

The NCCN guideline on Cutaneous Melanoma (v2.2021) 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.

Central Nervous System Cancers

The NCCN guideline on Central Nervous System Cancers (v2.2021) 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.

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

The NCCN guideline on epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer (v1.2021) 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.

Prostate Cancer

The NCCN guideline on prostate cancer (v1.2022) 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.

Pancreatic Cancer

The NCCN guideline on pancreatic cancer (v2.2021) recommends MSI testing and/or MMR testing for all patients with locally advanced or metastatic pancreatic adenocarcinoma.

Gastric Cancer

The NCCN guideline on gastric cancer (v1.2021) 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.

Esophageal and Esophagogastric Junction Cancer

The NCCN guideline on esophageal and esophagogastric junction cancer (v1.2021) recommends MSI by PCR, MMR by IHC, PD-L1 and HER2 testing if metastatic disease is documented/suspected.

Occult Primary

The NCCN guideline on occult primary (v1.2022) 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.

Testicular Cancer

The NCCN guideline for testicular cancer (v1.2021) recommends MSI testing in individuals with testicular cancer who have had progression after high-dose chemotherapy or third line therapy.

Chronic Lymphocytic Leukemia/Small lymphocytic Leukemia

Current NCCN guidelines for CLL/SLL (v1.2022) 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.

Gastrointestinal Stromal Tumors (GISTs)

Current NCCN guidelines (v1.2021) recommend KIT mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor.

American Society of Clinical Oncology (ASCO)

Colorectal Cancer

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.

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

Lung Cancer

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

Acute Leukemia

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).

Germline Testing and Somatic Mutation Profiling

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.

American College of Medical Genetics and Genomics:

Germline Implications of Somatic Mutation Profiling

ACMG (2020) published the following points to consider for clinical professionals in regard to the reporting of germline variation in patients undergoing tumor testing:

- Individuals undergoing tumor testing should undergo informed consent of the possibility that a PGPV might be discovered. However, if there is a clinical indicator for germline cancer predisposition, then dedicated germline testing should be ordered.
- Patient choice and autonomy (opt-out of PGPV result return) should be respected.
- When automated methods are used for pre- and posttesting education and counseling, clinicians with experience in cancer genetics should be available to answer specific questions.
- Patients should be informed that discovery of a PGPV would prompt referral for genetic consultation and the possibility of confirmatory germline testing.
- Confirmatory germline testing should be performed in a clinical laboratory that has adequate resources and expertise in conducting germline testing and interpreting and reporting the test results.
- Positive germline test results should be returned by qualified and experienced clinicians (e.g., oncologists with genetics expertise, geneticists, and genetic counselors).

ACMG (2020) published the following points to consider for laboratory professionals in regard to the reporting of germline variation in patients undergoing tumor testing:

- There are three tumor testing strategies: tumor-only testing, tumor-normal paired testing with germline variant subtraction, or tumor-normal paired testing with full analysis of the germline data from a subset of genes associated with cancer predisposition.
- Tumor-normal paired testing is not a substitute for dedicated germline testing unless the germline application was designed, validated, and implemented as part of the tumor-normal paired testing protocol.

- A known founder variant in a cancer predisposition gene detected on tumor-only testing is almost always germline, but still merits orthogonal confirmation.
- Copy-number variation and variant characteristics such as large indels or homopolymers may affect variant allele frequencies and may require specialized testing methods to report.
- Clinical data such as tumor type, age at cancer onset, bilateral or multiple tumors, and family history of cancer can help inform the evaluation of PGPVs.
- Using “normal” adjacent tissue in tumor-normal paired testing should be discouraged to avoid the risk of false positives/negatives due to field “cancerization” effects.
- Clonal hematopoiesis of indeterminate potential (CHIP) and aberrant clonal expansion (ACE) should be factored into genomic analyses, to minimize false-positive germline results or false-negative somatic results.

U.S. Food and Drug Administration (FDA):

Comprehensive Tumor Molecular Profiling Panels

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.

back to top

REFERENCES

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
2. Summary of Safety and Effectiveness Data (SSED): FoundationOne CDx™. U.S. Food & Drug Administration website. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2021. http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 8.2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
7. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(9):911-919. doi:10.1200/JCO.2017.76.7293
8. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 2.2022 https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf

10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Cancer. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GISTs). Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Systemic Mastocytosis. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf
16. Spaulding, T. P., Stockton, S. S., & Savona, M. R. (2020). The evolving role of next generation sequencing in myelodysplastic syndromes. British journal of haematology, 188(2), 224–239. https://doi.org/10.1111/bjh.16212
17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Uterine Neoplasms. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Chronic Myeloid Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Pediatric Acute Lymphoblastic Leukemia. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf
21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Acute Lymphoblastic Leukemia. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in B-Cell Lymphomas. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Hairy Cell Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Central Nervous System Cancers. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
25. Li MM, Chao E, Esplin ED, et al. Points to consider for reporting of germline variation in patients undergoing tumor testing: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(7):1142-1148. doi:10.1038/s41436-020-0783-8
26. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245. doi:10.1200/JCO.19.02960
27. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. 2015;33(31):3660-3667. doi:10.1200/JCO.2015.63.0996
28. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol. 2015;33(2):209-217. doi:10.1200/JCO.2014.58.1322
29. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Mol Diagn. 2017;19(2):187-225. doi:10.1016/j.jmoldx.2016.11.001
30. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
34. de Haas V, Ismaila N, Advani A, et al. Initial Diagnostic Work-Up of Acute Leukemia: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists and American Society of Hematology Guideline [published correction appears in J Clin Oncol. 2019 Mar 1;37(7):612]. J Clin Oncol. 2019;37(3):239-253. doi:10.1200/JCO.18.01468
35. Decision Summary: EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets). U.S. Food & Drug Administration website. Available at: https://www.accessdata.fda.gov/cdrh_docs/reviews/den170058.pdf
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
37. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 5.2021. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
38. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary [CUP]). Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
39. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
40. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
41. Pfeifer JD, Liu J. Rate of occult specimen provenance complications in routine clinical practice. Am J Clin Pathol. 2013;139(1):93-100. doi:10.1309/AJCP50WEZHWIFCIV
42. Pfeifer JD, Zehnbauer B, Payton J. The changing spectrum of DNA-based specimen provenance testing in surgical pathology. Am J Clin Pathol. 2011;135(1):132-138. doi:10.1309/AJCPLNO4PFVZVA4P
43. Marberger M, McConnell JD, Fowler I, et al. Biopsy misidentification identified by DNA profiling in a large multicenter trial. J Clin Oncol. 2011;29(13):1744-1749. doi:10.1200/JCO.2010.32.1646

44. Wojno K, Hornberger J, Schellhammer P, Dai M, Morgan T. The clinical and economic implications of specimen provenance complications in diagnostic prostate biopsies. J Urol. 2015;193(4):1170-1177. doi:10.1016/j.juro.2014.11.019
45. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf
46. Cushing MM, DeSimone RA, Goel R, et al. The impact of Daratumumab on transfusion service costs. Transfusion. 2019;59(4):1252-1258. doi:10.1111/trf.15134
47. Anani WQ, Marchan MG, Bensing KM, et al. Practical approaches and costs for provisioning safe transfusions during anti-CD38 therapy. Transfusion. 2017;57(6):1470-1479. doi:10.1111/trf.14021
48. Dizon MF. The Challenges of Daratumumab in Transfusion Medicine. Lab Med. 2017;48(1):6-9. doi:10.1093/labmed/lmw055
49. National Cancer Institute. Dictionary of Cancer Terms. Accessed 3/24/2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/advanced-cancer

back to top