Clinical Policy: Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies

Reference Number: CP.MP.241
Date of Last Revision: 02/22

Coding Implications
Revision Log

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

Description

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.

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
0037U	FoundationOne CDx (Foundation Medicine)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
0048U	MSK-IMPACT (Memorial Sloan Kettering Medical Center)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
0211U	MI Cancer Seek - NGS Analysis (Caris Life Sciences	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
0244U	Oncotype MAP™ PanCancer Tissue Test	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	FoundationOne Heme (Foundation Medicine)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	MI Profile (Caris Life Sciences)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	OmniSeq (Integrated Oncology)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	OnkoSight (GenPath)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	Tempus|xT (Tempus)	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	SmartGenomics	Comprehensive Molecular Profiling Panels for Solid Tumors	C00-D49, Z85
81455	FoundationOne Heme (Foundation Medicine)	Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	C91, C92
81450	NeoTYPE Myeloid Disorders Profile (NeoGenomics Laboratories) OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies (Mayo Medical Laboratories) Onkosight Myeloid Disorder Panel (BioReferences Laboratories)	Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	C91, C92
0111U	PraxisTM Extended RAS Panel (Illumina)	Colorectal Cancer Focused Molecular Profiling Panels	C18-C20

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81301, 81445	SmartGenomics NGS Colon (PathGroup) Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)	Colorectal Cancer Focused Molecular Profiling Panels	C18-C20
0022U	Oncomine Dx Target Test (Thermo Fisher)	Lung Cancer Focused Molecular Profiling Panels	C34
81445	Lung Cancer Panel (ARUP Laboratories) OnkoSight Lung Comprehensive (Bioreference Laboratories)	Lung Cancer Focused Molecular Profiling Panels	C34
81210, 81273, 81311, 81403, 81404, 81445, 88363	Melanoma Panel (Knight Diagnostics) OnkoSight Melanoma Panel (Bioreference Laboratories) Symgene Focus - NGS Melanoma (CellNetix Pathology and Laboratory)	Cutaneous Melanoma Focused Molecular Profiling Panels	C43, D03
0050U	MyAML NGS Panel (LabPMM, Invivoscribe Technologies)	Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	C92, D47
81450	Legacy AML Molecular Profile (NeoGenomics) LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)	Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	C92, D47
81206, 81207, 81208, 81270, 81219, 81402, 81403	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories MPN, JAK2/MPL/CALR by NGS (BioReferences Laboratories)	Myeloproliferative Neoplasms (MPNs) Focused Molecular Profiling Panel	C91, C92, D45, D47

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81170	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	ABL1 Kinase Domain Analysis	C92.1
81206, 81207, 81208	BCR/ABL1 Quantitative Analysis, BCR/ABL1 Qualitative Analysis, BCR/ABL1 P190 Quantitation, BCR/ABL1 P210 Quantitation	BCR/ABL Breakpoint Analysis	C83, C85, C91, C92, D45, D46
0016U	BCR-ABL1 major and minor breakpoint fusion transcripts (University of Iowa)	BCR/ABL Breakpoint Analysis	C83, C85, C91, C92, D45, D46
0040U	MRDx BCR-ABL Test (MolecularMD)	BCR/ABL Breakpoint Analysis	C83, C85, C91, C92, D45, D46
81210	BRAF V600E Targeted Mutation Analysis	BRAF Variant Analysis	C18-C20, C24, C43, C71, C73, C91.4
81162, 81163, 81164, 81165, 81166, 81167, 81216	BRCA1 Mutation Analysis BRCA2 Mutation Analysis BRCA1/2 Mutation Analysis	BRCA1/2 Variant Analysis	C56, C61
81219	CALR Sequencing Analysis	CALR Variant Analysis	C91, C92, C94, D45, D47.1, D47.3, D75.81
81218	CEBPA Targeted Mutation Analysis	CEBPA Variant Analysis	C92
81235	EGFR Targeted Mutation Analysis	EGFR Variant Analysis	C34
81245, 81246	FLT3 ITD Variant Analysis FLT3 TKD Variant Analysis	FLT3 Variant Analysis	C92
0023U	LeukoStrat CDx FLT3 Mutation Assay (LabPMM, Invivoscribe Technologies)	FLT3 Variant Analysis	C92

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
0046U	FLT3 ITD MRD by NGS (LABPMM, Invivoscribe Technologies)	FLT3 Variant Analysis	C92
81120, 81121	IDH1 Variant Analysis IDH2 Variant Analysis	IDH1 and IDH2 Variant Analysis	C71, D49.6
81261, 81262, 81263	IGHV Variant Analysis	IGHV Variant Analysis	C83, C91
0027U	JAK2 Exons 12 to 15 Sequencing (Mayo Clinic)	JAK2 Variant Analysis	C91, C92, C94, D45, D47.1, D47.3, D75.81
0017U	JAK2 Mutation (University of Iowa)	JAK2 Variant Analysis	C91, C92, C94, D45, D47.1, D47.3, D75.81
81270	JAK2 Targeted Mutation Analysis	JAK2 Variant Analysis	C91, C92, C94, D45, D47.1, D47.3, D75.81
81272, 81273	KIT Targeted Mutation Analysis	KIT Variant Analysis	C43, C49, D47.02
81275, 81276, S3713	KRAS Targeted Mutation Analysis	KRAS Variant Analysis	C18-20
81287	MGMT Methylation Analysis	MGMT Promoter Methylation Analysis	C71
81288	MLH1 Methylation Analysis	MLH1 Promoter Methylation Analysis	C18-C20, C54.1
81402, 81403	MPL Targeted Mutation Analysis	MPL Variant Analysis	C91, C92, C94, D45, D47.1, D47.3, D75.81
81301	Microsatellite Instability Analysis	Microsatellite Instability Analysis	C15, C17-C20, C25, C54.1, D44.10-44.12
0049U	NPM1 MRD by NGS (LabPMM, Invivoscribe Technologies)	NPM1 Variant Analysis	C92.20- C92.22

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81310	NPM1 Targeted Mutation Analysis	NPM1 Variant Analysis	C92.20- C92.22
81311	NRAS Targeted Mutation Analysis	NRAS Variant Analysis	C18-C20
81309	PIK3CA Targeted Mutation Analysis	PIK3CA Variant Analysis	C50, C55
0155U, 0177U	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	PIK3CA Variant Analysis	C50, C55
81404, 81405, 81406	RET Targeted Mutation Analysis RET Sequencing Analysis	RET Variant Analysis	C34, C73
81405	TP53 Sequencing Analysis	TP53 Variant Analysis	C92, R71, R79
0171U	MyMRD® NGS Panel, Laboratory for Personalized Medicine	Measurable (Minimal) Residual Disease (MRD) Analysis	C91, R71, R79
81479	ClonoSEQ (Adaptive Biotechnologies)	Measurable (Minimal) Residual Disease (MRD) Analysis	C91, R71, R79
0013U	MatePair Targeted Rearrangements, Oncology (Mayo Medical Laboratories)	Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	C00-D49, Z85
0014U	MatePair Targeted Rearrangements, Hematologic (Mayo Medical Laboratories)	Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	C00-D49, Z85
0056U	MatePair Acute Myeloid Leukemia Panel (Mayo Medical Laboratories)	Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	C00-D49, Z85
0036U	EXaCT-1 Whole Exome Testing (Weill Cornell Medicine)	Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	C00-D49, Z85
81415, 81416	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	Exome and Genome Sequencing in Solid Tumors and Hematologic Malignancies	C00-D49, Z85

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	GPS Cancer (NantHealth)		
81265, 81266, 81479	know error® DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC)	Genetic Testing to Confirm the Identity of Laboratory Specimens	C00.0-C80.2
0007U	ToxProtect (Genotox Laboratories LTD)	Genetic Testing to Confirm the Identity of Laboratory Specimens	C00.0-C80.2
0079U	ToxLok™ (InSource Diagnostics)	Genetic Testing to Confirm the Identity of Laboratory Specimens	C00.0-C80.2

This policy document provides criteria for *Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*. Please refer to:

- ***CP.MP.240 Oncology: Cytogenetic Testing*** for criteria related to tumor testing with IHC, FISH, etc (e.g., ALK, BCR/ABL FISH analysis, ERBB2 [HER2] IHC analysis, NTRK fusion analysis, ROS1 analysis)
- ***CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***CP.MP.238 Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- ***CP.MP.239 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.
- ***CP.MP.237 Oncology: Algorithmic Testing*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***CP.MP.219 Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders*** for criteria related to whole genome and whole exome sequencing in rare genetic syndromes.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to tumor and hematologic malignancy testing that is not specifically discussed in this or another non-general policy.

Policy/Criteria

Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies

Comprehensive Molecular Profiling Panels for Solid Tumors

I. It is the policy of health plans affiliated with Centene Corporation® that comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 81445, 81455) is considered **medically necessary** when meeting all of the following:

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

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

   C. One of the following:

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

      2. The member/enrollee *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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 81445, 81455) for all other indications.

Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

I. It is the policy of health plans affiliated with Centene Corporation® that comprehensive molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) is considered **medically necessary** when meeting any of the following:

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

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

      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),

         b) Thyroid disease,

         c) Drug-induced cytopenia,

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

C. The member/enrollee was suspected to have a myeloproliferative neoplasm, and both of the following:

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

2. Clinical suspicion for a myeloid neoplasm remains high,

D. The member/enrollee has a diagnosis of chronic myelogenous leukemia, and both of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support comprehensive molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) for all other indications.

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

Colorectal Cancer Focused Molecular Profiling Panels

I. It is the policy of health plans affiliated with Centene Corporation® that colorectal cancer focused molecular profiling panels (0111U, 81301, 81445) in solid tumors is considered **medically necessary** when meeting all of the following:

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

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

C. One of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support colorectal cancer-focused molecular profiling panels (0111U, 81301, 81445) for all other indications.

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

Lung Cancer Focused Molecular Profiling Panels

I. It is the policy of health plans affiliated with Centene Corporation® that lung cancer focused molecular profiling panels (0022U, 81445) is considered **medically necessary** when meeting all of the following:

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

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

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

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

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

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

   C. One of the following:

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

      2. The member/enrollee *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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support lung cancer-focused molecular profiling panels (81445, 0022U) for all other indications.

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

Cutaneous Melanoma Focused Molecular Profiling Panels

I. It is the policy of health plans affiliated with Centene Corporation® that cutaneous melanoma focused molecular profiling panels (81210, 81273, 81311, 81403, 81404, 81445) is considered **medically necessary** when meeting all of the following:

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

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

   C. One of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support cutaneous melanoma focused molecular profiling panels (81210, 81273, 81311, 81403, 81404, 81445) for all other indications.

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

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

I. It is the policy of health plans affiliated with Centene Corporation® that 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/enrollee has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support acute myeloid leukemia focused molecular profiling panels (81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) for all other indications.

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

Myeloproliferative Neoplasms (MPNs) Molecular Profiling Panel

I. It is the policy of health plans affiliated with Centene Corporation® that myeloproliferative neoplasm (MPN) molecular profiling panel (81206, 81207, 81208, 81270, 81219, 81402, 81403) is considered **medically necessary** when meeting both of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support myeloproliferative neoplasm (MPN) molecular profiling panel (81206, 81207, 81208, 81270, 81219, 81402, 81403) analysis for all other indications.

Single-Gene Testing Of Solid Tumors And Hematologic Malignancies

ABL1 Kinase Domain Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *ABL1* kinase domain analysis (81170) in hematologic malignancies is considered **medically necessary** when meeting both of the following:

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

B. Any of the following:

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

BCR/ABL1 Breakpoint Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *BCR/ABL1* breakpoint analysis (0016U, 0040U, 81206, 81207, 81208) in hematologic malignancies is considered **medically necessary** when meeting either of the following:

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

B. The member/enrollee is undergoing workup for or to monitor disease progression of any of the following:

1. Acute lymphoblastic leukemia (ALL),
2. Acute myeloid leukemia (AML),
3. Chronic myelogenous leukemia (CML),
4. Lymphoblastic leukemia.

BRAF Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies is considered **medically necessary** when meeting either of the following:

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

1. Suspected or proven metastatic, synchronous or metachronous colorectal cancer,
2. Advanced or metastatic non-small-cell lung cancer (NSCLC),
3. Stage III or stage IV cutaneous melanoma,
4. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma,
5. Low-grade glioma or pilocytic astrocytoma,

B. The member/enrollee is being evaluated for:

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

BRCA1/2 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors is considered **medically necessary** when:

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

1. Ovarian, fallopian tube and/or primary peritoneal cancer,

2. Metastatic prostate cancer.

CALR Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *CALR* variant analysis (81219) in solid tumors or hematologic malignancies is considered **medically necessary** when:

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

CEBPA Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *CEBPA* variant analysis (81218) in solid tumors or hematologic malignancies is considered **medically necessary** when:

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

EGFR Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *EGFR* variant analysis (81235) in solid tumors is considered **medically necessary** when:

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

1. Advanced or metastatic lung adenocarcinoma,

2. Advanced or metastatic large cell lung carcinoma,

3. Advanced or metastatic squamous cell lung carcinoma,

4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

FLT3 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in solid tumors or hematologic malignancies is considered **medically necessary** when meeting either of the following:

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

   B. The member/enrollee has a diagnosis of acute lymphoblastic leukemia (ALL) and previous testing for BCR-ABL1 was negative.

IDH1 and *IDH2* Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors is considered **medically necessary** when:

   A. The member/enrollee has a diagnosis of a glioma.

IGHV Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *IGHV* variant analysis (81261, 81262, 81263) in hematologic malignancies is considered **medically necessary** when:

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

      1. Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL),

      2. Primary cutaneous B-cell lymphoma,

      3. Mantle cell lymphoma,

      4. Post-transplant lymphoproliferative disorder.

JAK2 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies is considered **medically necessary** when:

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

KIT Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that Somatic *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies is considered **medically necessary** when meeting any of the following:

A. The member/enrollee is suspected to have, or is being worked up for, systemic mastocytosis,

B. The member/enrollee has a diagnosis of acute leukemia,

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

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

KRAS Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *KRAS* variant analysis (81275, 81276, S3713) in solid tumors is considered **medically necessary** when meeting either of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support 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).

MGMT Promoter Methylation Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *MGMT* promoter methylation analysis (81287) in solid tumors is considered **medically necessary** when:

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

1. Anaplastic oligodendroglioma,

2. Anaplastic oligoastrocytoma,

3. Anaplastic astrocytoma,

4. Anaplastic glioma,

5. Glioblastoma.

MLH1 Promoter Methylation Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *MLH1* promoter methylation analysis (81288) in solid tumors is considered **medically necessary** when meeting both of the following:

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

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

MPL Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *MPL* variant analysis (81402, 81403) in or hematologic malignancies is considered **medically necessary** when:

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

Microsatellite Instability Analysis (MSI)

I. It is the policy of health plans affiliated with Centene Corporation® that somatic microsatellite instability (MSI) analysis (81301) in solid tumors is considered **medically necessary** when:

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

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

NPM1 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *NPM1* variant analysis (81310, 0049U) in hematological malignancies is considered **medically necessary** when:

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

NRAS Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *NRAS* variant analysis (81311) in solid tumors is considered **medically necessary** when:

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

PIK3CA Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *PIK3CA* variant analysis (81309, 0155U, 0177U) in solid tumors is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee has recurrent or stage IV, HR positive, HER2 negative invasive breast cancer,

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

RET Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic *RET* variant analysis (81404, 81405, 81406) in solid tumors is considered **medically necessary** when meeting either of the following:

   A. The member/enrollee has a diagnosis of medullary thyroid cancer,

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

TP53 Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that somatic ***TP53*** variant analysis (81405) in bone marrow or peripheral blood is considered **medically necessary** when meeting either of the following:

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

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

Measurable (Minimal) Residual Disease (MRD) Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that measurable (minimal) residual disease analysis (0171U, 81479) in bone marrow or peripheral blood is **medically necessary** when:

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

      1. Acute Lymphoblastic Leukemia (ALL),
      2. Multiple Myeloma,
      3. Chronic Lymphoblastic Leukemia

Red Blood Cell Genotyping in Multiple Myeloma

I. It is the policy of health plans affiliated with Centene Corporation® that red blood cell genotyping (81479, 0001U, 0180U, 0221U) in individuals with multiple myeloma is considered **medically necessary** when meeting all of the following:

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

   B. The member/enrollee is currently being treated with Daratumumab (DARA),

   C. One of the following:

      1. Auto- or allo-antibodies are detected,
      2. RBC phenotyping cannot be performed due to a transfusion within the prior three months.

Whole Exome and Whole Genome Sequencing in Cancer

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support whole exome sequencing and whole genome sequencing in solid tumors (0013U, 0036U, 81415, 81416) and hematologic malignancies (0014U, 0056U, 81425, 81426).

Genetic Testing to Confirm the Identity of Laboratory Specimens

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support genetic testing to confirm the identity of laboratory specimens (e.g., know error, ToxProtect, ToxLok) (0007U, 0079U, 81265, 81266, 81479), when billed separately, because it is generally considered to be an existing component of the genetic testing process for quality assurance.

Medically Necessary Tumor Testing By Cancer Type:

Cancer Type	**Molecular Analysis** (see 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

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)

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.

Background

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 Lymphoblastic Leukemia
The NCCN guidelines on pediatric acute lymphoblastic 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 Lymphoblastic Leukemia
The NCCN guidelines on acute lymphoblastic 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 lymphoblastic 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.

<u>American College of Medical Genetics and Genomics:</u>
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.

Coding Implications

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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Important Reminder

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

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

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

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

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

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

be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

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

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