BSC_CON_2.04	Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies		
Original Policy Date:	June 1, 2023	**Effective Date:**	November 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 57

Example Test Table

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

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies		
Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels	FoundationOne CDx (Foundation Medicine)	0037U
	MSK-IMPACT (Memorial Sloan Kettering Medical Center)	0048U
	Oncomap ExTra (Exact Sciences Laboratories, LLC)	0329U
	OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs)	81445, 81455, 81457, 81458
	Tempus xT (Tempus)	
	Precise Tumor (Myriad)	
	Guardant360 TissueNext (Guardant)	0334U
	PGDx elio tissue complete (Personal Genome Diagnostics, Inc)	0250U
	OmniSeq INSIGHT (Labcorp)	81455
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)	
	Solid Tumor Expanded Panel (Quest Diagnostics)	0379U
	UW OncoPlex Cancer Gene Panel (University of Washington)	81459
	Strata Select (Strata Oncology)	0391U
Targeted RNA Fusion Panels	Targeted Solid Tumor NGS Fusion Panel (NeoGenomics)	81449, 81451
Broad RNA Fusion Panels	Tempus xR Whole Transcriptome RNA Sequencing (Tempus)	81456
	Aventa FusionPlus (Aventa Genomics)	0444U
Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81450, 81455
	Tempus xT Hematologic Malignancy (Tempus)	
	Neo Comprehensive - Myeloid Disorders (NeoGenomics Laboratories)	
	MayoComplete Myeloid Neoplasms, Comprehensive OncoHeme Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)	81450
	Onkosight Advanced NGS Myeloid Panel (BioReference Laboratories)	

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Colorectal Cancer Focused Molecular Profiling Panels	Praxis Extended RAS Panel (Illumina)	0111U
	Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)	81445
	COLONSEQPlus Panel (MedFusion)	81457
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test (Thermo Fisher Scientific)	0022U
	OnkoSight Advanced Lung Cancer NGS Panel (BioReference Laboratories)	81457
Cutaneous Melanoma Focused Molecular Profiling Panels	MelanomaSeqPlus (Quest Diagnostics)	81445
	OnkoSight Advanced Melanoma NGS Panel (BioReference Laboratories)	81457
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML NGS Gene Panel Assay (Laboratory for Personalized Molecular Medicine)	0050U
	NeoTYPE AML Prognostic Profile (NeoGenomics)	81450
	LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)	
Myeloproliferative Neoplasms (MPNs) Panel Tests	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories)	81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339
	OnkoSight Advanced NGS JAK2, MPL, CALR Panel (BioReference Laboratories)	
Single Gene Testing of Solid Tumors and Hematologic Malignancies		
Tumor Specific *BCR/ABL1* Kinase Domain Analysis	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170
	Onkosight NGS ABL1 Sequencing (BioReference Laboratories)	
Tumor Specific *BCR/ABL1* FISH, Qualitative,and Quantitative Tests	BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics)	81206, 81207, 81208
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (Labcorp)	
	BCR/ABL1 (t9;22)) RNA Quantitative with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology)	0016U
	MRDx BCR-ABL Test (MolecularMD)	0040U
	Detection by FISH of t(9;22) BCR/ABL (CGC Genetics)	81479, 88271, 88274, 88275, 88291
	BCR/ABL t(9;22) (NeoGenomics Laboratories)	
	BCR ABL Qualitative (Cincinnati Children's Hospital)	
Tumor Specific *BRAF* Variant Analysis	BRAF Mutation Analysis (NeoGenomics)	81210
Tumor Specific *BRCA1/2* Variant Analysis	BRCA1/2 Mutation Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81162, 81163, 81164, 81165, 81166, 81167, 81216
	BRCA1/2 Mutation Analysis for Tumors (NeoGenomics Laboratories)	
Tumor Specific *CALR* Variant Analysis	Calreticulin (CALR) Mutation Analysis (Quest Diagnostics)	81219

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Tumor Specific *CEBPA* Variant Analysis	CEBPA Mutation Analysis (Labcorp)	81218
Tumor Specific *EGFR* Variant Analysis	EGFR Mutation Analysis (NeoGenomics Laboratories)	81235
Tumor Specific *ESR1* Variant Analysis	ESR1 Mutations Analysis, NGS, Tumor (Mayo Clinic Laboratories)	81479
Tumor Specific *FLT3* Variant Analysis	FLT3 ITD and TKD Mutation (PCR) (PathGroup)	81245, 81246
	LeukoStrat CDx FLT3 Mutation Assay (Versiti)	0023U
	FLT3 ITD MRD Assay (Laboratory for Personalized Molecular Medicine)	0046U
Tumor Specific *IDH1* and *IDH2* Variant Analysis	IDH1/IDH2 Mutation Analysis by PCR (NeoGenomics)	81120, 81121
Tumor Specific *IGHV* Somatic Hypermutation Analysis	IgVH Mutation Analysis (NeoGenomics)	81261, 81262, 81263
Tumor Specific *JAK2* Variant Analysis	JAK2 Exon 12 to 15 Sequencing, Polycythemia Vera Reflex, Varies (Mayo Clinic Laboratories)	0027U
	JAK2 Mutation (University of Iowa)	0017U
	JAK2 V617F Mutation Analysis (Quest Diagnostics)	81270
Tumor Specific *KIT* Variant Analysis	KIT Mutation Analysis (ProPath)	81272, 81273
	KIT (D816V) Digital PCR in Systemic Mastocytosis (Labcorp)	
Tumor Specific *KRAS* Variant Analysis	KRAS Mutation Analysis (NeoGenomics)	81275, 81276
Tumor Specific *MGMT* Methylation Analysis	MGMT Promoter Methylation -Tumor (Ohio State University Molecular Pathology Laboratory)	81287
Tumor Specific *MLH1* Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics)	81288
Tumor Specific *MPL* Variant Analysis	MPL Mutation Analysis (Quest Diagnostics)	81338, 81339
Tumor Specific Microsatellite Instability (MSI) Analysis	Microsatellite Instability (MSI) by PCR (NeoGenomics)	81301
	Microsatellite Instability (MSI) (Quest Diagnostics)	
Tumor Specific *NPM1* Variant Analysis	NPM1 MRD Assay (Laboratory for Personalized Molecular Medicine)	0049U
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)	81310
Tumor Specific *NRAS* Variant Analysis	NRAS Mutation Analysis (NeoGenomics)	81311
Tumor Specific *PIK3CA* Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309
	PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp)	0155U
Tumor Specific *TP53* Variant Analysis	TP53 Mutation Analysis (NeoGenomics Laboratories)	81352
Measurable (Minimal) Residual Disease (MRD) Analysis		
Hematologic Minimal Residual Disease (MRD) Analysis	MyMRD NGS Panel Assay(Laboratory for Personalized Molecular Medicine)	0171U
	ClonoSEQ Assay (Adaptive Biotechnologies)	0364U
Solid Tumor Minimal Residual	Signatera - Residual Disease Test (MRD) - (Natera)	0340U

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Disease (MRD) Analysis	Personalized Cancer MonitoringBaseline Test (Invitae)	0306U
	Personalized Cancer Monitoring - Monitoring TestD (Invitae)	0307U
	RaDaR (NeoGenomics)	81479
	Colvera (Clinical Genomics Pathology)	0229U
	Guardant360 Response (Guardant Health)	0422U
Tumor Mutational Burden (TMB)		
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479
Red Blood Cell Genotyping in Multiple Myeloma		
Red Blood Cell Genotyping in Multiple Myeloma	PreciseType HEA (Immucor)	0001U
	Navigator ABO Sequencing (Grifols Immunohematology Center)	0180U
	Navigator ABO Blood Group NGS (Grifols Immunohematology Center)	0221U
Cancer Exome and Genome Sequencing		
Cancer Exome/Genome Sequencing	Praxis Somatic Whole Genome Sequencing (Praxis Genomics)	0297U
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	81415, 81416, 81425, 81426
	Tempus xE (Tempus)	
	EXaCT-1 Whole Exome Testing (Weill Cornell Medicine)	0036U
Genetic Testing to Confirm the Identity of Laboratory Specimens		
Genetic Testing to Confirm the Identity of Laboratory Specimens	know error DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC)	81265, 81266, 81479

Policy Statement

Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

I. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when:
   A. The member has a diagnosis of:
      1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**
      2. Histiocytosis**, OR**
      3. Non-small cell lung cancer (NSCLC) regardless of stage, **AND**
   B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**
   C. The member has a diagnosis of uterine neoplasm, **AND**
      1. The member is undergoing initial evaluation, **OR**
   D. The member has resectable or borderline resectable pancreatic adenocarcinoma, **AND**
      1. The member is being considered for systemic therapy.

II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when:
   A. The member has progression of **any** of the following:
      1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**
      2. Advanced or metastatic gastric adenocarcinoma, **OR**
      3. Metastatic prostate cancer.

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

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

Targeted RNA Fusion Panels

IV. RNA specific fusion panels with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449, 81451) may be considered **medically necessary** when **any** of the following are met:
   A. The member has a diagnosis of or is undergoing workup for **any** of the following:
      1. Adult or pediatric acute lymphoblastic leukemia (ALL)
      2. Glioma
      3. Histiocytosis
      4. Sarcoma
   B. The member has a gastrointestinal stromal tumor, **AND**
      1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations
   C. The member has non-small cell lung cancer, **AND**
      1. DNA based NGS tumor profiling was negative for actionable mutations
   D. The member has a metastatic or advanced solid tumor, **AND any** of the following:
      1. There is a fusion-targeted therapy with regulatory approval for that cancer type
      2. DNA-based panel testing was negative for oncogenic driver mutations.

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

Broad RNA Fusion Panels

VI. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) may be considered **medically necessary** when:
   A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL).

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

Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met:
   A. The member has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML)
   B. The member has newly diagnosed acute lymphoblastic leukemia (ALL)
   C. The member has newly diagnosed myelodysplastic syndrome (MDS)
   D. The member has suspected myelodysplastic syndrome (MDS) **AND**
      1. Other causes of cytopenia(s) have been ruled out

E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following:
   1. This is the member's initial genetic evaluation for suspected MPN
   2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative

F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following:
   1. There has been progression to accelerated or blast phase
   2. Results of *BCR-ABL1* kinase domain mutation analysis were negative.

IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when:
   A. The member has myelodysplastic syndrome (MDS), **AND**
      1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR**
   B. The member has acute lymphoblastic leukemia (ALL), **AND**
      1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR**
   C. The member has acute myeloid leukemia (AML), **AND**
      1. The member has relapsed or refractory disease or progression on treatment.

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

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

Colorectal Cancer Focused Molecular Profiling Panels

XI. Colorectal cancer focused molecular profiling panels (0111U, 81445, 81457) in solid tumors may be considered **medically necessary** when:
   A. The member has suspected or proven metastatic colorectal cancer, **AND**
   B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.*

XII. Colorectal cancer-focused molecular profiling panels (0111U, 81445, 81457) are considered **investigational** for all other indications.

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

Lung Cancer Focused Molecular Profiling Panels

XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be 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
      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), **AND**
   B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy).

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

XV. Lung cancer-focused molecular profiling panels (0022U, 81457) are considered **investigational** for all other indications.

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

Cutaneous Melanoma Focused Molecular Profiling Panels

XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) may be considered **medically necessary** when **all** of the following are met:
- A. The member has a new diagnosis of stage IV melanoma or has recurrent melanoma
- B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy)
- 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
  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.

XVII. Cutaneous melanoma focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications.

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

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

XVIII. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) may be considered **medically** necessary when:
- A. The member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).

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

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

Myeloproliferative Neoplasms (MPNs) Panels

XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:
- A. The member 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*.

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

Single-Gene Testing Of Solid Tumors And Hematologic Malignancies
Tumor Specific *BCR/ABL1* Kinase Domain Analysis

XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met:
- A. The member has a diagnosis of chronic myeloid leukemia (CML) or Philadelphia Ph-like acute lymphocytic leukemia (ALL)
- B. The member has **any** of the following:
  1. Inadequate initial response to TKI therapy
  2. Loss of response to TKI therapy

3. Disease progression to the accelerated or blast phase
4. Relapsed/refractory disease.

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

XXIII. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 88271, 88274, 88275, 88291, 81479) in hematologic malignancies may be considered **medically necessary** when **any** of the following are met:
- A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia)
- B. The member is undergoing diagnostic workup for **any** of the following:
  1. Acute lymphoblastic leukemia (ALL)
  2. Acute myeloid leukemia (AML)
  3. Chronic myeloid leukemia (CML)
  4. B-cell lymphoma
- C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following:
  1. Acute lymphoblastic leukemia (ALL)
  2. Acute myeloid leukemia (AML)
  3. Chronic myelogenous leukemia (CML)
  4. B-cell lymphoma.

Tumor Specific *BRAF* Variant Analysis

XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when:
- A. The member has a diagnosis of **any** of the following:
  1. Suspected or proven metastatic colorectal cancer,
  2. Advanced or metastatic non-small-cell lung cancer (NSCLC)
  3. Stage III or stage IV cutaneous melanoma
  4. Indeterminate thyroid nodules requiring biopsy
  5. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinom
  6. Low-grade glioma or pilocytic astrocytoma
  7. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma
  8. Metastatic small bowel adenocarcinoma
- B. The member is being evaluated for **any** of the following:
  1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype)
  2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).

Tumor Specific *BRCA1/2* Variant Analysis

XXV. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors may be considered **medically necessary** when:
- A. The member has a diagnosis of **any** of the following:
  1. Ovarian, fallopian tube and/or primary peritoneal cancer
  2. Metastatic prostate cancer
  3. Resectable, borderline resectable, or locally advanced/metastatic pancreatic cancer.

Tumor Specific *CALR* Variant Analysis

XXVI. Tumor specific *CALR* variant analysis (81219) may be 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).

Tumor Specific *CEBPA* Variant Analysis

XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when:
- A. The member has cytogenetically normal acute myeloid leukemia (AML).

Tumor Specific *EGFR* Variant Analysis

XXVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when:
- A. The member has a diagnosis of **any** of the following:
  1. Stage IB or higher lung adenocarcinoma
  2. Stage IB or higher large cell lung carcinoma
  3. Stage IB or higher squamous cell lung carcinoma
  4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

Tumor Specific *ESR1* Variant Analysis

XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors may be considered **medically necessary** when **all** of the following are met:
- A. The member is a postmenopausal female or adult male
- B. The member has a diagnosis of ER-positive and HER2-negative breast cancer
- C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

Tumor Specific *FLT3* Variant Analysis

XXX. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in hematologic malignancies may be considered **medically necessary** when:
- A. The member has suspected or confirmed acute myeloid leukemia (AML), **OR**
- B. The member has a diagnosis of **any** of the following:
  1. Acute lymphocytic leukemia (ALL)
  2. Myelodysplastic syndrome (MDS),
  3. Myeloproliferative neoplasm.

Tumor Specific *IDH1* and *IDH2* Variant Analysis

XXXI. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when:
- A. The member has a diagnosis of:
  1. Glioma, **OR**
  2. Acute myeloid leukemia (AML).

Tumor Specific *IGHV* Somatic Hypermutation Analysis

XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when:
- A. The member has a diagnosis of **any** of the following:
  1. Chronic lymphocytic leukemia (CLL)
  2. Small lymphocytic leukemia (SLL)
  3. Primary cutaneous B-cell lymphoma
  4. Mantle cell lymphoma
  5. Post-transplant lymphoproliferative disorder.

Tumor Specific *JAK2* Variant Analysis

XXXIII. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:

A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia)
B. The member has acute lymphoblastic leukemia (ALL)
C. The member is suspected to have a myelodysplastic syndrome (MDS).

Tumor Specific *KIT* Variant Analysis

XXXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:
A. The member is suspected to have, or is being evaluated for systemic mastocytosis
B. The member has a diagnosis of acute myeloid leukemia (AML)
C. The member has stage IV cutaneous melanoma, **OR**
D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST).

Tumor Specific *KRAS* Variant Analysis

XXXV. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when **any** of the following criteria are met:
A. The member has suspected or proven metastatic colorectal cancer
B. The member is undergoing workup for metastasis of non-small cell lung cancer
C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.

Tumor Specific *MGMT* Methylation Analysis

XXXVI. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. High grade (stage III or IV) anaplastic oligodendroglioma
2. High grade (stage III or IV) anaplastic astrocytoma
3. High grade (stage III or IV) anaplastic glioma
4. High grade (stage III or IV) glioblastoma.

Tumor Specific *MLH1* Methylation Analysis

XXXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when:
A. The member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND**
B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis.

Tumor Specific *MPL* Variant Analysis

XXXVIII. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when:
A. The member is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).

Tumor Specific Microsatellite Instability (MSI) Analysis

XXXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. Colorectal cancer
2. Endometrial cancer
3. Gastric cancer
4. Esophageal and esophagogastric junction cancer
5. Recurrent, progressive or metastatic cervical carcinoma

6. Testicular cancer (nonseminoma) with progression after high dose chemotherapy or third-line therapy
7. Unresectable or metastatic gallbladder cancer
8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma
9. Unresectable or metastatic breast cancer
10. Small bowel adenocarcinom
11. Resectable, borderline resectable, or metastatic pancreatic cancer
12. Metastatic occult primary
13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva.

Tumor Specific *NPM1* Variant Analysis

XL. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when:
   A. The member has cytogenetically normal acute myeloid leukemia (AML).

Tumor Specific *NRAS* Variant Analysis

XLI. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when:
   A. The member has suspected or proven metastatic colorectal cancer.

Tumor Specific *PIK3CA* Variant Analysis

XLII. Tumor specific *PIK3CA* variant analysis (81309, 0155U) in solid tumors may be considered **medically necessary** when **either** of the following are met:
   A. The member has a diagnosis of recurrent or stage IV, HR positive, HER2 negative invasive breast cancer
   B. The member has a diagnosis of uterine rhabdomyosarcoma.

Tumor Specific *TP53* Variant Analysis

XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when **either** of the following are met:
   A. The member has a diagnosis of **any** of the following:
      1. Acute myeloid leukemia (AML)
      2. Chronic lymphocytic leukemia (CLL)
      3. Small lymphocytic leukemia (SLL)
   B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL).

Measurable (Minimal) Residual Disease (MRD) Analysis

Hematologic Minimal Residual Disease (MRD) Testing

XLIV. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when:
   A. The member has a diagnosis of **any** of the following:
      1. Acute Lymphocytic Leukemia (ALL)
      2. Multiple Myeloma
      3. Chronic Lymphocytic Leukemia (CLL)

Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing

XLV. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue may be considered **medically necessary** when **all** of the following are met:
   A. The member has a personal history of metastatic colorectal or breast cancer, or muscle invasive bladder cancer
   B. The identification of recurrence or progression of disease will require a change in management

C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method,
D. The member meets **one** of the following:
   1. The member is currently being treated for cancer, **AND**
      a. The test has not previously been done for this episode of cancer
   2. The member is not currently being treated for their cancer, **AND**
      a. The test has not been done in the past 12 months, **OR**
   3. The member is being monitored for response to immune checkpoint inhibitor therapy, **AND**
      a. The test has not previously been ordered for this episode of cancer, **AND**
      b. The member has **either** of the following:
         i. Colorectal cancer, for which Guardant360 Response is being performed, **OR**
         ii. Any solid tumor, for which Signatera is being performed.

XLVI. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated.

HPV-Related Solid Tumor Measurable (Minimal) Residual Disease (MRD) Testing

XLVII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers may be **medically necessary** when **all** of the following are met:
A. The member has a personal history of HPV-driven oropharyngeal cancer
B. The identification of recurrence or progression of disease will require a change in management
C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method,
D. The member meets **one** of the following:
   1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND**
      a. The test has not previously been done for this episode of cancer, **OR**
   2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND**
      a. The test has not been done in the past 12 months.

XLVIII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers is considered **investigational** for all other indications.

Tumor Mutational Burden (TMB)

XLIX. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
   1. Recurrent or metastatic breast cancer
   2. Unresectable or metastatic gallbladder cancer
   3. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma
   4. Suspected metastatic malignant occult primary tumor
   5. Recurrent ovarian/fallopian tube/primary peritoneal cancer
   6. Resectable or borderline resectable or metastatic or advanced pancreatic adenocarcinoma
   7. Metastatic castration-resistant prostate cancer
   8. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy
   9. Endometrial carcinoma or uterine sarcoma
   10. Locally advanced/metastatic ampullary adenocarcinoma
   11. Metastatic chondrosarcoma
   12. Metastatic chordoma

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

Red Blood Cell Genotyping In Multiple Myeloma

L. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when **both** of the following are met:
   A. The member has a diagnosis of multiple myeloma
   B. The member is currently being treated or will be treated with Daratumumab (DARA).

Cancer Exome And Genome Sequencing

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

Genetic Testing To Confirm The Identity Of Laboratory Specimens

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Definitions

1. **Tumor mutational burden:** A measurement of mutations carried by tumor cells and is a predictive biomarker that is being studied to evaluate its association with response to immunotherapy.
2. **Advanced cancer:** Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Myeloproliferative Neoplasms:** Rare overlapping blood diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets.

There are seven subcategories of myeloproliferative neoplasms:

- Chronic myeloid leukemia (CML)
- Polycythemia vera (PV)

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

4. **Myelodysplastic Syndromes (MDS):** A group of disorders characterized by abnormalities of the bone marrow, leading to low numbers of one or more types of blood cells. The WHO system recognizes 6 main types of MDS:
   - MDS with multilineage dysplasia (MDS-MLD)
   - MDS with single lineage dysplasia (MDS-SLD)
   - MDS with ring sideroblasts (MDS-RS)
   - MDS with excess blasts (MDS-EB)
   - MDS with isolated del(5q)
   - MDS, unclassifiable (MDS-U)
5. **Widely metastatic cancer:** A cancer for which local control cannot be delivered to all areas of disease (per NCCN guidelines).

Coding
See the Codes table for details.

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 aid in making a diagnosis of a specific type of malignancy. For solid tumors, molecular analysis can be performed via direct testing of the tumor (which is addressed in this policy) or via circulating tumor DNA or circulating tumor cells (CTCs) (see Other Related Policies). For hematologic malignancies, molecular analysis can be performed on blood samples or bone marrow biopsy samples.

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

While the primary goal of the molecular analysis of solid tumors and hematologic malignancies is to identify biomarkers that diagnose or to give prognostic and treatment selection information, this testing also has the potential to uncover clinically relevant germline variations that are associated with a hereditary cancer susceptibility syndrome, and other conditions, if confirmed to be present in the germline. Current tumor testing strategies include tumor-only testing, tumor-normal paired testing with germline variant subtraction, and tumor-normal paired testing with explicit analysis of a group of genes associated with germline cancer predisposition. This is an evolving area and clear guidelines around the optimal approach for identification and reporting of the presumed germline pathogenic variants (PGPVs) are emerging.

The genetic testing of tumors and hematologic malignancies (somatic mutation profiling) may reveal incidental germline findings or suspicion of a clinically significant germline mutation. Providers should communicate the potential for these incidental findings with their patients prior to somatic mutation profiling. Clinical decision making should not be made based on variants of uncertain significance.

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

Related Policies

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

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

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Rationale

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Breast Cancer (1.2024) recommend comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer. (p. BINV-18)
The NCCN guideline on Occult Primary (1.2024) recommends MSI and MMR testing as part of the initial work up for patients with cancer of unknown primary. The guideline further recommends consideration of NGS to identify actionable genomic aberrations after a histological determination of the tumor has been made. (p. OCC-1)

The NCCN guideline on Non-Small Cell Lung Cancer (2.2024) has several recommendations regarding biomarker testing:

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

The NCCN guideline for Colon Cancer (1.2024) recommends all patients with metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. Testing can be performed on the primary tumor and/or metastases (p. COL-B 4 of 8)

The NCCN guideline for Gastric Cancer (3.2023) recommends that patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering an FDA approved therapy undergo comprehensive genomic profiling via a validated NGS assay for the identification of *HER2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions, *RET* gene fusions, and *BRAF* V600E mutations when limited diagnostic tissue is available or patient can't undergo a traditional biopsy. The guidelines also recommend that repeat tumor testing can be considered when there is clinical or radiologic evidence for disease progression of advanced gastric cancer. (p. GAST-B 5 of 6)

The NCCN guideline for Ovarian Cancer Including Fallopian Tumor Cancer and Primary Peritoneal Cancer (1.2024) recommends that patients with recurrent disease, tumor molecular analysis have at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor specific or tumor-agnostic benefit. (p OV-6) More comprehensive testing may be particularly important in less

common histologies with limited approved therapeutic options. (p. OV-B 1 of 3) These guidelines also recommend that molecular testing be performed on the most recent tumor tissue available. (p. OV-8)
The NCCN guideline for Pancreatic Adenocarcinoma (1.2024) recommends tumor/somatic molecular profiling for patients with resectable or borderline resectable, or local advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. They also recommend considering specifically testing for potentially actionable somatic findings including but not limited to fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations *BRAF, BRCA1/2*, *KRAS*, *PALB2*, amplifications (*HER2*), MSI, and or mismatch repair deficiency. (p. PANC-1A, PANC-F, 1 of 12)
The NCCN guideline for Prostate Cancer (4.2023) recommends somatic tumor testing and states that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. The guidelines also recommend that repeat tumor profiles can be considered at the time of progression of disease. They also recommend tumor testing for alterations in homologous recombination DNA report genes such as *BRCA1/2, ATM, PALB2, FANCA, RAD512D, CHEK2, CDK12*, is for patients with metastatic prostate cancer. (p. PROS-C 3 of 3)
The NCCN guideline for Histiocytic Neoplasms (1.2023) recommends targeted-capture, next generation sequencing (NGS) in the work-up/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD). or both LCH and ECD, NCCN notes that molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. (p. LCH-2, ECD-2 For RDD, NCCN recommends targeted-capture, next-generation sequencing (NGS) for mutations in the MAPK pathway and in other molecular pathways. (p. RDD-1)

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

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

Targeted RNA Fusion Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) and Pediatric Acute Lymphoblastic Leukemia (3.2024) recommends comprehensive testing during the diagnostic workup by next generation sequencing for gene fusions and pathogenic mutations, especially for Ph-like ALL, which is associated with recurrent gene fusions in the tyrosine kinase pathways. Targeted testing for these abnormalities at diagnosis may aid in risk stratification. (p. ALL-1, p. PEDALL-1) Per the NCCN Biomarker Compendium, testing for gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, or *PDGFRB* and mutations involving *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions) is recommended for this indication.

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

NCCN guidelines for Non-Small Cell Lung Cancer (2.2024) state that for patients who don't have identifiable driver oncogenes via broad panel testing, RNA-based NGS testing should be considered if not already performed, to maximize detection of fusion events as fusions involving *ROS1*, *MET* and *RET* have better detection using RNA based methods.(p. NSCL-H, 2, 4, 5 of 7).

NCCN guidelines for Soft Tissue Sarcoma (3.2023) state that while morphologic diagnosis remains the gold standard for sarcoma diagnosis, molecular genetic testing using NGS based methods including DNA and RNA sequencing is an ancillary approach that can be helpful depending on type of tumor. (p. SARC-C, 1 of 4).

NCCN guidelines for Histiocytic Neoplasms (1.2023) recommends molecular testing for somatic mutations and fusions in the workup for Langerhans Cell Histiocytosis, (p. LCH-1), Erdheim-Chester Disease, (p. ECD-1) and Rosai-Dorfman Disease (p. RDD-1). RNA-based molecular panels including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements.

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

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

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

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

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

Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Acute Myeloid Leukemia (6.2023) recommends testing for patients over the age of 18 that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses. (p.EVAL-1) Multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (p. EVAL-1A) The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) state that patients diagnosed with acute lymphoblastic leukemia should undergo molecular characterization including comprehensive testing by NGS for gene fusions and pathogenic mutations which may aid in risk stratification. (p. ALL-1) Additionally, patients who are undergoing surveillance after maintenance therapy and are showing evidence of symptomatic relapse should undergo repeat testing. (p. ALL-6)

The NCCN guidelines for Myelodysplastic Syndromes (3.2023) recommends the following:

- Genetic testing for somatic mutations (i.e., acquired mutations) in genes associated with myelodysplastic syndromes should be performed for suspected myelodysplasia. (p. MDS-1)
- Additionally, patients who have persistent cytopenia (at least 4-6 months) and lack other underlying conditions that could cause cytopenia should be evaluated for myelodysplastic syndromes. (p. MDS-3)
- Several gene mutations have been identified among patients with MDS that may, in part, contribute to the clinical heterogeneity of the disease course, and thereby influence the

prognosis of patients. Such gene mutations will be present in the majority of newly diagnosed patients, including most patients with normal cytogenetics. (p. MS-18)
- Repeat molecular testing is recommended if a member has relapsed after allo-HCT [hematopoietic cell transplant]. (p. MDS-6 and MDS-6A)

The NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommend for patients suspected of having an MPN to have molecular testing for *JAK2* V617F*, CALR* and *MPL* mutations for patient with symptoms of essential thrombocythemia or myelofibrosis, and *JAK2* exon 12 mutations for patients with polycythemia vera. This testing can be done in a stepwise manner, or as an NGS multigene panel. (p. MPN-1)

The NCCN guidelines for Chronic Myeloid Leukemia (2.2024) indicate that a patient with advanced phase CML in either accelerated or blast phase should consider mutational analysis with a myeloid mutation panel (CML-1). Patients on TKI therapy who have progressed to accelerated or blast phase should consider a myeloid mutation panel to identify *BCR-ABL-1*-independent resistance mutations in patients with no *BCR-ABL1* kinase domain mutations. (p. CML-E)

Colorectal Cancer Focused Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guideline for Colon Cancer (1.2024) recommends all patients with suspected or proven metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-2) The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types. (p. COL-B, 4 of 8) In addition, patients with documented metachronous metastases should have determination of tumor gene status for *RAS* and *BRAF* mutations. (p. COL-9)
The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS, NRAS,* and *BRAF* mutations are similar in both specimen types.

Lung Cancer Focused Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guideline for Non-Small Cell Lung Cancer (2.2024) recommends at this time that when feasible, testing be performed via a broad, panel-based approach, most typically performed by NGS. For patients who, in broad panel testing do not have identifiable driver oncogenes (especially in never smokers), consider RNA-based NGS if not already performed, to maximize detection of fusion events. (p. NSCL-H 2 OF 7)

Cutaneous Melanoma Focused Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Cutaneous Melanoma (3.2023) state that *BRAF* and *KIT* testing should be performed for initial presentation with stage IV disease or clinical recurrence, but broader genomic profiling (such as larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT*, *BRAF* non-V600). (p. ME-C 4 of 8)

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

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (6.2023) recommends for patients over the age of 18 testing that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses including molecular analysis. (p.EVAL-1) Multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (p. EVAL-1A)

Myeloproliferative Neoplasms (MPNs) Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (3.2023) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts be performed to exclude the diagnosis of CML. Additionally, molecular testing for *JAK2* mutations is recommended in initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MPN-1)

Tumor Specific *BCR/ABL1* Kinase Domain Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Chronic Myeloid Leukemia (2.2024) outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, including *BCR/ABL1* tests for diagnosis, monitoring, and *ABL1* kinase domain single nucleotide variants. *BCR/ABL1* kinase domain mutation analysis is recommended, among other times, when patients fail to meet milestones related to disease response, the disease has progressed to the accelerated or blast phase, or there are clinical signs of loss of complete cytogenetic response. (p. CML-E)

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) recommend *ABL1* kinase domain mutation testing for patients with relapsed/refractory, Philadelphia chromosome positive (Ph+) B-ALL. (p. ALL-9, p. ALL-1) Similar recommendations are made in the NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (3.2024). (p. PEDALL-1 and PEDALL-1A)

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

National Comprehensive Cancer Network (NCCN)

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

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

The NCCN guidelines on B-cell Lymphomas (1.2024) include PCR for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphoblastic lymphoma. (p. BLAST-1)

The NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommend evaluation for *BCR-ABL1* via FISH or multiplex RT-PCR to exclude a diagnosis of CML. (p. MPN-1)

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

The NCCN guidelines for Chronic Myeloid Leukemia (2.2024) recommend quantitative RT-PCR testing for *BCR/ABL1* for patients undergoing work-up for CML. (p. CML-1)

Tumor Specific *BRAF* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Thyroid Carcinoma (4.2023) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS. Additionally, they comment that molecular testing has shown to be beneficial when making targeted therapy decisions. The guideline also comments that individuals with anaplastic thyroid cancer and/or metastatic disease should undergo molecular testing including *BRAF, NTRK, ALK, RET* and tumor mutational burden if not previously done. (p. ANAP-1, p. PAP-9, p. FOLL-8, p. HURT-8)
The NCCN guideline on Hairy Cell Leukemia (1.2024) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL [classical hairy cell leukemia]immunophenotype. (p. HCL-1)

The NCCN guideline on Cutaneous Melanoma (3.2023) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. (ME-C 4 of 8)

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

The NCCN guidelines for Non-Small Cell Lung Cancer (1.2024) recommend molecular testing including *BRAF* analysis for advanced or metastatic adenocarcinoma, large cell, NSCLC not otherwise specified, or squamous cell carcinoma. (p. NSCL-18)

The NCCN guidelines for Colon Cancer (1.2024) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma. (p. COL-2)
NCCN guidelines for Histiocytic Neoplasms (1.2023) recommends *BRAF* V600E testing (IHC or PCR) from biopsy tissue during the workup for Langerhans cell histiocytosis or Erdheim-Chester disease. (p. LCH-1, ECD-1)

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

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

Tumor Specific *BRCA1/2* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (1.2024) recommends that all patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should have genetic risk evaluation and germline and somatic testing of *BRCA1* and *BRCA2* if not previously done. (p. OV-1) In addition to *BRCA1/2* testing, other methods for evaluating HR deficiency status (e.g., genomic instability, loss of heterozygosity) can be considered.

Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor specific or tumor-agnostic targeted therapy options exist. (p. OV-B 1 of 3)

The NCCN guideline on Prostate Cancer (4.2023) recommend evaluating tumor for alterations in homologous recombination DNA repair genes such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2* and *CDK12* in patients with metastatic prostate cancer and tumor testing for MSI-H and/or dMMR can be considered. (p. PROS-C, 3 of 3)

The NCCN guideline on Pancreatic Cancer (1.2024) recommends molecular profiling of tumor tissue for patients with resectable, borderline resectable, or locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), etc. (p. PANC-1 and PANC-1A)
American Society of Clinical Oncology (ASCO)

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

- All women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting. (Recommendation 1.2, p. 6)

Tumor Specific *CALR* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) state that FISH or RT-PCR to detect *BCR-ABL1* transcripts is recommended to exclude the diagnosis of CML (p. MS-6). Additionally, they recommend that molecular testing for *JAK2* mutations is recommended in initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MS-7 and MPN-1)

Tumor Specific *CEBPA* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Acute Myeloid Leukemia (6.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *EGFR* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Non-Small Cell Lung Cancer (2.2024) state that molecular testing for *EGFR* mutations should be performed when adjuvant TKI therapy is a consideration for NSCLC stage IB–IIIA, IIIB [T3,N2]. Testing should also be performed for advanced or metastatic disease preferably by broad molecular profiling (p. NSCL-18). While the testing process may be technically easier on a

resection specimen, initial diagnostic biopsy specimens are also acceptable for testing for this indication. (p. NSCL-H, 3 of 7)

Tumor Specific *ESR1* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Breast Cancer (1.2024) recommend that post-menopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutation positive breast cancer that have progressed following one or two lines of endocrine therapy, including one line containing a CDK4/6 inhibitor, be considered for treatment with Elacestrant. (p. BINV-Q 6 of 14)

Tumor Specific *FLT3* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Acute Myeloid Leukemia (6.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) and Pediatric Acute Lymphoblastic Leukemia (3.2024) indicate that comprehensive testing for gene fusions and pathogenic mutations using NGS sequencing is recommended for molecular prognostic risk stratification and that *FLT3* mutations confer poor or unfavorable risk. (p. ALL-1, ALL-3, PEDALL-1, PEDALL-A, 1 of 2)
The NCCN guidelines on Myelodysplastic Syndromes (3.2023) highly recommends genetic testing for somatic mutations in genes associated with myelodysplastic syndromes, which includes *FLT3* (p. MDS-1, MDS-C, 1 of 3).

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

Tumor Specific *IDH1* and *IDH2* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Acute Myeloid Leukemia (6.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications, including *IDH1/IDH2.* (p. EVAL-1)
The NCCN guideline on Central Nervous System Cancers (1.2023) states that *IDH* mutation testing (*IDH1* and *IDH2*) is required for the work-up for all gliomas. (p. BRAIN-F 2 of 10)

Tumor Specific *IGHV* Somatic Hypermutation Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (1.2024) state that molecular testing for the immunoglobulin heavy chain variable region gene (*IGHV*) is useful for prognostic and/or therapy determination. (p. CSLL-1)

The NCCN B-cell Lymphomas guidelines (1.2024) recommend *IGHV* sequencing for individuals with mantle cell lymphoma, (p. MANT-1) These guidelines also state that molecular analysis of immunoglobulin gene rearrangements can be useful under some circumstances for patients with post-transplant lymphoproliferative disorders. (p. PTLD-1)

The NCCN Primary Cutaneous Lymphomas guidelines (1.2024) state that flow cytometry or IGH gene rearrangement studies can be of use for patients with primary cutaneous B-cell lymphoma, if adequate biopsy material is available. (p. CUTB-1)

Tumor Specific *JAK2* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) recommend molecular testing for *JAK2* mutations in the initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MS-7)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (3.2024) recommend that those with the Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2*, or *PDGFRB* and mutations involving *FLT3, IL7R, SH2B3, JAK1, JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. (p. ALL-1A)

The NCCN guidelines for Myelodysplastic Syndromes (3.2023) list JAK2 as a potentially mutated gene in MDS. (p. MDS-C 2 of 3)

Tumor Specific *KIT* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Cutaneous Melanoma (3.2023) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. They further recommend that if feasible, broader genomic profiling with NGS panels be performed in individuals with stage IV or recurrent melanoma especially if the test results could guide future treatment options. (p. ME-C, 4 of 8)

NCCN guidelines for Gastrointestinal Stromal Tumors (1.2023) recommend *KIT* mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor. (p. GIST-B)
The NCCN guideline on Acute Myeloid Leukemia (6.2023) recommends all patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. Presently, *c-KIT*, *FLT3*-ITD, *FLT3*-TKD, *NPM1*, *CEBPA* (biallelic), *IDH1*/*IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* alpha are included in this group. (p. MS-3)

The NCCN guidelines for Systemic Mastocytosis (1.2024) recommends that all patients presenting with signs or symptoms of mastocytosis undergo molecular testing for *KIT* mutations. (p. SM-1)

Tumor Specific *KRAS* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Colon Cancer (1.2024) all patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor. (p.COL-B 4 of 8)

The NCCN guideline on Non-Small Cell Lung Cancer (2.2024) strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. The

following genes are recommended - *EGFR* mutation, *ALK*, *KRAS, ROS1, BRAF*, *NTRK1/2/3, METex14* skipping, *RET, ERBB2 (HER2).* (p. NSCL- 18)

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

Tumor Specific *MGMT* Methylation Analysis

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

Tumor Specific *MLH1* Methylation Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Genetic/Familial High-Risk Assessment: Colorectal (2.2023) states that patients with colorectal or endometrial (uterine) cancer with tumors that show abnormal MLH1 IHC should have testing for *MLH1* promoter methylation. Hypermethylation of the *MLH1* promoter in these tumors has been associated with sporadic cancer, and not Lynch syndrome. (p. LS-A 1 of 8)

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

- Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines. (p. 210)
- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of *BRAF* V600E mutation or analysis of methylation of the *MLH1* promoter should be carried out first to rule out a sporadic case. If the tumor is MMR deficient and somatic *BRAF* mutation is not detected or *MLH1* promoter methylation is not identified, testing for germline mutations is indicated. (p. 210)

Tumor Specific *MPL* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Myeloproliferative Neoplasms (1.2024) recommends molecular testing (blood or bone marrow) for *JAK2* V617F mutation; if negative, test for *CALR* and *MPL* mutations (for patients with essential thrombocythemia and myelofibrosis) and *JAK2* exon 12 mutations (for patients, with polycythemia vera) or molecular testing using multigene NGS panel that includes *JAK2*, *CALR*, and *MPL*. (p. MPN-1).

Tumor Specific Microsatellite Instability (MSI) Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Colon Cancer (1.2024) recommend determination of tumor MMR and MSI in all individuals with colorectal cancer. (p. COL-B 4 of 8)

The NCCN guidelines for Uterine Neoplasms (1.2024) recommend MSI (among other studies) for patients with endometrial carcinoma. (p. ENDO-A 2 of 4)

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

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

The NCCN guidelines for Cervical Cancer (1.2024) recommend MSI testing for patients with progressive, recurrent, or metastatic disease. (p. CERV-A 1 of 3)

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

The NCCN guidelines for Biliary Tract Cancers (3.2023) recommends MSI testing for unresectable or metastatic gallbladder cancer (p. GALL-5) or unresectable or metastatic intrahepatic cholangiocarcinoma (p. INTRA-1) or extrahepatic cholangiocarcinoma. (p. EXTRA-1)

The NCCN guidelines for Breast Cancer (1.2024) can be considered for patients with unresectable or metastatic breast cancer when considering pembrolizumab as treatment. (p. BINV-R 1 of 3)

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

The NCCN guidelines for an Occult Primary (1.2024) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology. (p. OCC-1)
The NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend MSI (among other studies) for patients with metastatic pancreatic cancer (p. PANC-1A) or resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12).

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

Tumor Specific *NPM1* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Acute Myeloid Leukemia (6.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *NRAS* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guideline on Colon Cancer (1.2024) recommends that all patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. (p. COL-B 4 of 8)

Tumor Specific *PIK3CA* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Breast Cancer (1.2024) recommends that recurrent or stage IV HR-positive/HER2-negative breast cancers be assessed for *PIK3CA* mutations with tumor or liquid biopsy to identify candidates for Alpelisib + fulvestrant. They also recommend that recurrent or stage

IV MSH-H/dMMR breast cancers that have progressed following prior treatment be considered for treatment with Pembrolizumab. (p. BINV-R 1 of 3)
The NCCN guidelines on Uterine Neoplasms (1.2024) state that *PIK3CA* mutations can be found in pleomorphic uterine rhabdomyosarcomas. (p. UTSARC-A 7 of 8)

Tumor Specific *TP53* Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Acute Myeloid Leukemia (6.2023) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

The NCCN guidelines on B-cell Lymphoma (1.2024) recommend *TP53* mutation analysis for patients with a diagnosis of mantle cell lymphoma in order to direct treatment selection, as patients with a *TP53* mutation have been associated with poor prognosis when treated with conventional therapy. (p. MANT-1)

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (1.2024) recommend *TP53* sequencing analysis and *IGHV* mutation analysis to inform prognosis and therapeutic options for patients diagnosed with CLL/SLL or upon progression or recurrence (p. CSLL-1). Minimal residual disease testing at the end of treatment for CLL is recommended. (p. CSLL-2, 2 of 2)

MEASUREABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS

Hematologic Minimal Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2023) recommend baseline flow cytometric and/or molecular characterization of leukemic clone(s) to facilitate subsequent minimal/measurable residual disease (MRD) analysis (p. ALL-1). After treatment induction, MRD is recommended to determine consolidation therapy (p. ALL-3). For surveillance on bone marrow aspirate, MRD assessment is recommended. (p. ALL-6)

The NCCN guidelines for Multiple Myeloma (2.2024) recommend consideration of MRD testing by NGS in the initial diagnostic workup (p. MYEL-1) or follow up/surveillance, prognostication. (p. MYEL-4)

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (1.2024) recommend minimal residual disease testing at the end of treatment for CLL/SLL. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method. (p. CSLL-E 1 of 2)

Solid Tumor Minimal Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)
Per the NCCN Colon Cancer guidelines (1.2024), "There is currently insufficient evidence to recommend routine use of circulating tumor DNA (ctDNA) assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results. Participation in clinical trials is encouraged." (p. COL-4)

The Colon Cancer guidelines also add that "...the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore,

the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy." (MS-22)

The NCCN Breast Cancer guidelines (1.2024) state the following: "The clinical use of Circulating Tumor Cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring. (p. MS-75)

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

Tumor Mutational Burden (TMB)
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Breast Cancer (1.2024) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. BINV-Q)

The NCCN guidelines for Biliary Tract Cancers (3.2023) recommend tumor mutational burden testing for unresectable or metastatic gallbladder cancer. (p. GALL-5) These guidelines also recommend tumor mutational burden testing for unresectable or metastatic intrahepatic cholangiocarcinoma (p. INTRA-1) and unresectable or metastatic extrahepatic cholangiocarcinoma. (p. EXTRA-1)

The NCCN guidelines for Occult Primary Cancers (1.2024) recommends consideration of tumor mutational burden testing for patients with suspected metastatic malignancy of uncertain pathology. (p. OCC-1)

The NCCN guidelines for Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (1.2024) recommend tumor analysis, including tumor mutational burden, for recurrent ovarian/Fallopian tube/primary peritoneal cancer. (p. OV-B 1 of 3)

The NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) recommend testing tumor mutational burden for patients with resectable, borderline resectable, or locally advanced and metastatic pancreatic cancer as pembrolizumab may be considered for treatment. (p. PANC-F, 1 of 12, 6 of 12)
The NCCN guideline for Prostate Cancer (4.2023) states that tumor mutational burden testing may be considered for patients with metastatic castration-resistant prostate cancer. (p. PROS-C 3 of 3)
The NCCN guidelines for Testicular Cancer (1.2023) recommend tumor mutational burden testing for patients with nonseminoma testicular cancer who have experienced disease progression after high-dose chemotherapy or third-line therapy. (p. TEST-15)

The NCCN guidelines for Uterine Neoplasms (1.2024) recommend consideration of tumor mutational burden testing for patients with endometrial cancer (p. ENDO-A 2 of 4). The guidelines also recommend tumor mutational burden testing be done for patients with uterine sarcoma. (p. UTSARC-A 1 of 8)

NCCN guidelines for Ampullary Adenocarcinoma (1.2024) recommend tumor/somatic molecular profiling for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2*, and *RET*), mutations (*BRAF, BRCA1/2, KRAS*, and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. (p. AMP-3)

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

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

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

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

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

NCCN guidelines for Thyroid Carcinoma (4.2023) state that genomic testing to identify actionable mutations and tumor mutational burden (TMB) should be done for patients with locally recurrent, advanced and/or metastatic papillary (p. PAP-10), follicular (p. FOLL-9) or oncocytic carcinoma (p. ONC-9) that is not amenable to RAI therapy, and for patients with stage IVC anaplastic carcinoma (p. ANAP-3).

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

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

Red Blood Cell Genotyping in Multiple Myeloma

Association for the Advancement of Blood and Biotherapies

The AABB (Association for the Advancement of Blood and Biotherapies; formerly known as the American Association of Blood Banks) published Association Bulletin #16-02 on January 15 2016 (updated April 2023) recommending that all patients should undergo baseline phenotype and genotype prior to initiation of anti-CD38 monoclonal antibody treatment (daratumumab) to mitigate the potential of anti-CD38 interference with serologic testing. The bulletin also notes that this genotyping can be performed after the initiation of treatment. (p. 2 and 3)

Cancer Exome and Genome Sequencing

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

Genetic Testing to Confirm the Identity of Laboratory Specimens

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

Centers for Medicare and Medicaid Services
The CMS local coverage determination (LCD) entitled "MolDX: Minimal Residual Disease Testing for Cancer" states the following regarding minimally invasive molecular DNA and RNA tests that detect minimal residual disease (MRD) in patients with a personal history of cancer:

1. The patient has a personal history of cancer, the type and staging of which is within the intended use of the MRD test;
2. The identification of recurrence or progression of disease within the intended use population of the test is identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management;
3. The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard-of-care for monitoring a given cancer type) of recurrence or progression;

When the patient is NOT known to have cancer (specifically when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer), a second kind of test may exist wherein a single timepoint may constitute a single test. In such patients, the frequency of MRD testing is in accordance with national or society guidelines or recommendations."

From the billing and coding article:
"Intended uses that have met clinical validity (CV) criteria under the policy include: (1) the diagnosis of disease progression, recurrence, or relapse for advanced colorectal (Natera and Guardant), bladder and breast cancers (Natera)....(3) the monitoring of response to immune-checkpoint inhibitor therapy for colorectal cancer (Guardant) or any solid tumor (Natera). However, the tests listed in the table may have only been approved for one or more (but not necessarily all) of these indications.
"Regarding the use of NGS-based MRD tests (i.e., Signatera) in patients with cancer– The service may be performed once per patient per cancer diagnosis, unless there is clinical evidence of *a priori* change in genetic content."

"Intended uses that have met clinical validity (CV) criteria under the policy include: ... (2) the diagnosis of disease recurrence or relapse for advanced breast (RaDaR) and HPV-driven oropharyngeal cancer (Naveris).... However, the tests listed in the table may have only been approved for one or more (but not necessarily all) of these indications."

Concert Note:
For use of minimal residual disease testing, absent clear, specific and evidence-based guideline recommendations for a particular regimen of testing, a default frequency of once per cancer diagnosis for patients with cancer or once every 12 months for patients without cancer will be adopted.

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements

are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported
	0007U	Drug test(s), presumptive, with definitive confirmation of positive results, any number of drug classes, urine, includes specimen verification including DNA authentication in comparison to buccal DNA, per date of service
	0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
	0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
	0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence or absence of variants and associated therapy(ies) to consider
	0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
	0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0040U	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	0046U	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
	0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
	0049U	NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, quantitative
	0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
	0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
	0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3- kinase, catalytic subunit alpha) (e.g., breast cancer) gene analysis (i.e., p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only],

Type	Code	Description
		p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status (PLA code for the therascreen® PIK3CA RGQ PCR Kit from QIAGEN)
	0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis
	0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
	0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD
	0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
	0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
	0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin[1]embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
	0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
	0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate
	0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications,

Type	Code	Description
		gene rearrangements, microsatellite instability, and tumor mutational burden
	0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splicesite variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
	0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability
	0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
	0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s) ***(Code effective 4/1/2024)***
	0450U	Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LC-MS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides ***(Code effective 7/1/2024)***
	0451U	Oncology (multiple myeloma), LC-MS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance ***(Code effective 7/1/2024)***
	0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden ***(Code effective 7/1/2024)***
	0511U	Oncology (solid tumor), tumor cell culture in 3D microenvironment, 36 or more drug panel, reported as tumor-response prediction for each drug ***(Code effective 10/1/2024)***
	0473U	Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden ***(Code effective 7/1/2024)***
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (e.g., glioma), common variants (e.g., R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (e.g., glioma), common variants (e.g., R140W, R172M)
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)

Type	Code	Description
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
	81207	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence
	81219	CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9
	81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81245	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)
	81246	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
	81263	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemia and lymphoma, B-cell), variable region somatic mutation analysis
	81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
	81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (e.g., additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
	81270	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

Type	Code	Description
	81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)
	81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
	81279	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)
	81287	MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme) promoter methylation analysis
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
	81310	NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
	81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R)
	81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10
	81352	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (e.g., 4 oncology)
	81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

Type	Code	Description
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability ***(Code effective 1/1/2024)***
	81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability ***(Code effective 1/1/2024)***
	81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements ***(Code effective 1/1/2024)***
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2023	New policy (combined policies 2.04.115, 2.04.124, and 2.04.60).
07/01/2023	Administrative update. Policy statement and guidelines updated.
09/01/2023	Administrative update. Policy statement and guidelines updated.
11/01/2023	Coding Update.
03/01/2024	Coding Update.
05/01/2024	Coding Update.
07/01/2024	Annual review. Policy statement, guidelines and literature updated.
09/01/2024	Coding Update.
11/01/2024	Coding Update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not

more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies BSC_CON_2.04 **Policy Statement:** **Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies** **Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels** I. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when: A. The member has a diagnosis of: 1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR** 2. Histiocytosis**, OR** 3. Non-small cell lung cancer (NSCLC) regardless of stage, **AND** B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR** C. The member has a diagnosis of uterine neoplasm, **AND** 1. The member is undergoing initial evaluation, **OR** D. The member has resectable or borderline resectable pancreatic adenocarcinoma, **AND** 1. The member is being considered for systemic therapy. II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when: A. The member has progression of **any** of the following: 1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR** 2. Advanced or metastatic gastric adenocarcinoma, **OR** 3. Metastatic prostate cancer.	**Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies BSC_CON_2.04** **Policy Statement:** **Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies** **Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels** I. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when: A. The member has a diagnosis of: 1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR** 2. Histiocytosis**, OR** 3. Non-small cell lung cancer (NSCLC) regardless of stage, **AND** B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR** C. The member has a diagnosis of uterine neoplasm, **AND** 1. The member is undergoing initial evaluation, **OR** D. The member has resectable or borderline resectable pancreatic adenocarcinoma, **AND** 1. The member is being considered for systemic therapy. II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when: A. The member has progression of **any** of the following: 1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR** 2. Advanced or metastatic gastric adenocarcinoma, **OR** 3. Metastatic prostate cancer.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
III. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **investigational** for all other indications. **Note**: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes. **Targeted RNA Fusion Panels** IV. RNA specific fusion panels with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449, 81451) may be considered **medically necessary** when **any** of the following are met: A. The member has a diagnosis of or is undergoing workup for **any** of the following: 1. Adult or pediatric acute lymphoblastic leukemia (ALL) 2. Glioma 3. Histiocytosis 4. Sarcoma B. The member has a gastrointestinal stromal tumor, **AND** 1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations C. The member has non-small cell lung cancer, **AND** 1. DNA based NGS tumor profiling was negative for actionable mutations D. The member has a metastatic or advanced solid tumor, **AND any** of the following: 1. There is a fusion-targeted therapy with regulatory approval for that cancer type 2. DNA-based panel testing was negative for oncogenic driver mutations. V. RNA specific fusion panels (81449, 81451) are considered **investigational** for all other indications.	III. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **investigational** for all other indications. **Note**: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes. **Targeted RNA Fusion Panels** IV. RNA specific fusion panels with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449, 81451) may be considered **medically necessary** when **any** of the following are met: A. The member has a diagnosis of or is undergoing workup for **any** of the following: 1. Adult or pediatric acute lymphoblastic leukemia (ALL) 2. Glioma 3. Histiocytosis 4. Sarcoma B. The member has a gastrointestinal stromal tumor, **AND** 1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations C. The member has non-small cell lung cancer, **AND** 1. DNA based NGS tumor profiling was negative for actionable mutations D. The member has a metastatic or advanced solid tumor, **AND any** of the following: 1. There is a fusion-targeted therapy with regulatory approval for that cancer type 2. DNA-based panel testing was negative for oncogenic driver mutations. V. RNA specific fusion panels (81449, 81451) are considered **investigational** for all other indications.

Broad RNA Fusion Panels VI. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) may be considered **medically necessary** when: A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL). VII. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) are considered **investigational** for all other indications.	**Broad RNA Fusion Panels** VI. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) may be considered **medically necessary** when: A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL). VII. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) are considered **investigational** for all other indications.
Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met: A. The member has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML) B. The member has newly diagnosed acute lymphoblastic leukemia (ALL) C. The member has newly diagnosed myelodysplastic syndrome (MDS) D. The member has suspected myelodysplastic syndrome (MDS) **AND** 1. Other causes of cytopenia(s) have been ruled out E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following: 1. This is the member's initial genetic evaluation for suspected MPN 2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following: 1. There has been progression to accelerated or blast phase 2. Results of *BCR-ABL1* kinase domain mutation analysis were negative.	**Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels** VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met: A. The member has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML) B. The member has newly diagnosed acute lymphoblastic leukemia (ALL) C. The member has newly diagnosed myelodysplastic syndrome (MDS) D. The member has suspected myelodysplastic syndrome (MDS) **AND** 1. Other causes of cytopenia(s) have been ruled out E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following: 1. This is the member's initial genetic evaluation for suspected MPN 2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following: 1. There has been progression to accelerated or blast phase 2. Results of *BCR-ABL1* kinase domain mutation analysis were negative.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when: A. The member has myelodysplastic syndrome (MDS), **AND** 1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR** B. The member has acute lymphoblastic leukemia (ALL), **AND** 1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR** C. The member has acute myeloid leukemia (AML), **AND** 1. The member has relapsed or refractory disease or progression on treatment.	IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when: A. The member has myelodysplastic syndrome (MDS), **AND** 1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR** B. The member has acute lymphoblastic leukemia (ALL), **AND** 1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR** C. The member has acute myeloid leukemia (AML), **AND** 1. The member has relapsed or refractory disease or progression on treatment.
X. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **investigational** for all other indications.	X. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **investigational** for all other indications.
Note: If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies.	**Note:** If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies.
Colorectal Cancer Focused Molecular Profiling Panels XI. Colorectal cancer focused molecular profiling panels (0111U, 81445, 81457) in solid tumors may be considered **medically necessary** when: A. The member has suspected or proven metastatic colorectal cancer, **AND** B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.*	**Colorectal Cancer Focused Molecular Profiling Panels** XI. Colorectal cancer focused molecular profiling panels (0111U, 81445, 81457) in solid tumors may be considered **medically necessary** when: A. The member has suspected or proven metastatic colorectal cancer, **AND** B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.*
XII. Colorectal cancer-focused molecular profiling panels (0111U, 81445, 81457) are considered **investigational** for all other indications.	XII. Colorectal cancer-focused molecular profiling panels (0111U, 81445, 81457) are considered **investigational** for all other indications.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Note: If a panel is performed, appropriate panel codes should be used. **Lung Cancer Focused Molecular Profiling Panels** XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be 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 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), **AND** B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy). XIV. Repeat lung cancer-focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer. XV. Lung cancer-focused molecular profiling panels (0022U, 81457) are considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. **Cutaneous Melanoma Focused Molecular Profiling Panels** XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) may be considered **medically necessary** when **all** of the following are met: A. The member has a new diagnosis of stage IV melanoma or has recurrent melanoma	**Note:** If a panel is performed, appropriate panel codes should be used. **Lung Cancer Focused Molecular Profiling Panels** XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be 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 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), **AND** B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy). XIV. Repeat lung cancer-focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer. XV. Lung cancer-focused molecular profiling panels (0022U, 81457) are considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. **Cutaneous Melanoma Focused Molecular Profiling Panels** XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) may be considered **medically necessary** when **all** of the following are met: A. The member has a new diagnosis of stage IV melanoma or has recurrent melanoma

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy) 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 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.	B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy) 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 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.
XVII. Cutaneous melanoma focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications.	XVII. Cutaneous melanoma focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications.
Note: If a panel is performed, appropriate panel codes should be used.	**Note:** If a panel is performed, appropriate panel codes should be used.
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels XVIII. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) may be considered **medically** necessary when: A. The member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).	**Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels** XVIII. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) may be considered **medically** necessary when: A. The member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).
XIX. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **investigational** for all other indications.	XIX. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **investigational** for all other indications.
Note: If a multigene panel is performed, appropriate panel codes should be used.	**Note:** If a multigene panel is performed, appropriate panel codes should be used.
Myeloproliferative Neoplasms (MPNs) Panels XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:	**Myeloproliferative Neoplasms (MPNs) Panels** XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
A. The member 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*.	A. The member 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*.
XXI. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **investigational** for all other indications.	XXI. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **investigational** for all other indications.
Single-Gene Testing Of Solid Tumors And Hematologic Malignancies **Tumor Specific *BCR/ABL1* Kinase Domain Analysis** XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met: A. The member has a diagnosis of chronic myeloid leukemia (CML) or Philadelphia Ph-like acute lymphocytic leukemia (ALL) B. The member has **any** of the following: 1. Inadequate initial response to TKI therapy 2. Loss of response to TKI therapy 3. Disease progression to the accelerated or blast phase 4. Relapsed/refractory disease.	**Single-Gene Testing Of Solid Tumors And Hematologic Malignancies** **Tumor Specific *BCR/ABL1* Kinase Domain Analysis** XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met: A. The member has a diagnosis of chronic myeloid leukemia (CML) or Philadelphia Ph-like acute lymphocytic leukemia (ALL) B. The member has **any** of the following: 1. Inadequate initial response to TKI therapy 2. Loss of response to TKI therapy 3. Disease progression to the accelerated or blast phase 4. Relapsed/refractory disease.
Tumor Specific *BCR/ABL1* FISH, Qualitative, or Quantitative Tests XXIII. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 88271, 88274, 88275, 88291, 81479) in hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) B. The member is undergoing diagnostic workup for **any** of the following:	**Tumor Specific *BCR/ABL1* FISH, Qualitative, or Quantitative Tests** XXIII. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 88271, 88274, 88275, 88291, 81479) in hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) B. The member is undergoing diagnostic workup for **any** of the following:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myeloid leukemia (CML) 4. B-cell lymphoma C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following: 1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myelogenous leukemia (CML) 4. B-cell lymphoma. **Tumor Specific *BRAF* Variant Analysis** XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Suspected or proven metastatic colorectal cancer, 2. Advanced or metastatic non-small-cell lung cancer (NSCLC) 3. Stage III or stage IV cutaneous melanoma 4. Indeterminate thyroid nodules requiring biopsy 5. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinom 6. Low-grade glioma or pilocytic astrocytoma 7. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma 8. Metastatic small bowel adenocarcinoma B. The member is being evaluated for **any** of the following: 1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype) 2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).	1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myeloid leukemia (CML) 4. B-cell lymphoma C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following: 1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myelogenous leukemia (CML) 4. B-cell lymphoma. **Tumor Specific *BRAF* Variant Analysis** XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Suspected or proven metastatic colorectal cancer, 2. Advanced or metastatic non-small-cell lung cancer (NSCLC) 3. Stage III or stage IV cutaneous melanoma 4. Indeterminate thyroid nodules requiring biopsy 5. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinom 6. Low-grade glioma or pilocytic astrocytoma 7. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma 8. Metastatic small bowel adenocarcinoma B. The member is being evaluated for **any** of the following: 1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype) 2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).

Tumor Specific *BRCA1/2* Variant Analysis XXV. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Ovarian, fallopian tube and/or primary peritoneal cancer 2. Metastatic prostate cancer 3. Resectable, borderline resectable, or locally advanced/metastatic pancreatic cancer.	**Tumor Specific *BRCA1/2* Variant Analysis** XXV. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Ovarian, fallopian tube and/or primary peritoneal cancer 2. Metastatic prostate cancer 3. Resectable, borderline resectable, or locally advanced/metastatic pancreatic cancer.
Tumor Specific *CALR* Variant Analysis XXVI. Tumor specific *CALR* variant analysis (81219) may be 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).	**Tumor Specific *CALR* Variant Analysis** XXVI. Tumor specific *CALR* variant analysis (81219) may be 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).
Tumor Specific *CEBPA* Variant Analysis XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when: A. The member has cytogenetically normal acute myeloid leukemia (AML).	**Tumor Specific *CEBPA* Variant Analysis** XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when: B. The member has cytogenetically normal acute myeloid leukemia (AML).
Tumor Specific *EGFR* Variant Analysis XXVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS).	**Tumor Specific *EGFR* Variant Analysis** XXVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Stage IB or higher lung adenocarcinoma 2. Stage IB or higher large cell lung carcinoma 3. Stage IB or higher squamous cell lung carcinoma 4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS).
Tumor Specific *ESR1* Variant Analysis XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors may be considered **medically necessary** when **all** of the following are met:	**Tumor Specific *ESR1* Variant Analysis** XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors may be considered **medically necessary** when **all** of the following are met:

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
A. The member is a postmenopausal female or adult male B. The member has a diagnosis of ER-positive and HER2-negative breast cancer C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.	A. The member is a postmenopausal female or adult male B. The member has a diagnosis of ER-positive and HER2-negative breast cancer C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.
Tumor Specific *FLT3* Variant Analysis XXX. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in hematologic malignancies may be considered **medically necessary** when: A. The member has suspected or confirmed acute myeloid leukemia (AML), **OR** B. The member has a diagnosis of **any** of the following: 1. Acute lymphocytic leukemia (ALL) 2. Myelodysplastic syndrome (MDS), 3. Myeloproliferative neoplasm.	**Tumor Specific *FLT3* Variant Analysis** XXX. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in hematologic malignancies may be considered **medically necessary** when: A. The member has suspected or confirmed acute myeloid leukemia (AML), **OR** B. The member has a diagnosis of **any** of the following: 1. Acute lymphocytic leukemia (ALL) 2. Myelodysplastic syndrome (MDS), 3. Myeloproliferative neoplasm.
Tumor Specific *IDH1* and *IDH2* Variant Analysis XXXI. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of: 1. Glioma, **OR** 2. Acute myeloid leukemia (AML).	**Tumor Specific *IDH1* and *IDH2* Variant Analysis** XXXI. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of: 1. Glioma, **OR** 2. Acute myeloid leukemia (AML).
Tumor Specific *IGHV* Somatic Hypermutation Analysis XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Chronic lymphocytic leukemia (CLL) 2. Small lymphocytic leukemia (SLL) 3. Primary cutaneous B-cell lymphoma 4. Mantle cell lymphoma 5. Post-transplant lymphoproliferative disorder.	**Tumor Specific *IGHV* Somatic Hypermutation Analysis** XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Chronic lymphocytic leukemia (CLL) 2. Small lymphocytic leukemia (SLL) 3. Primary cutaneous B-cell lymphoma 4. Mantle cell lymphoma 5. Post-transplant lymphoproliferative disorder.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Tumor Specific *JAK2* Variant Analysis XXXIII. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) B. The member has acute lymphoblastic leukemia (ALL) C. The member is suspected to have a myelodysplastic syndrome (MDS).	**Tumor Specific *JAK2* Variant Analysis** XXXIII. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) B. The member has acute lymphoblastic leukemia (ALL) C. The member is suspected to have a myelodysplastic syndrome (MDS).
Tumor Specific *KIT* Variant Analysis XXXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have, or is being evaluated for systemic mastocytosis B. The member has a diagnosis of acute myeloid leukemia (AML) C. The member has stage IV cutaneous melanoma, **OR** D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST).	**Tumor Specific *KIT* Variant Analysis** XXXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met: A. The member is suspected to have, or is being evaluated for systemic mastocytosis B. The member has a diagnosis of acute myeloid leukemia (AML) C. The member has stage IV cutaneous melanoma, **OR** D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST).
Tumor Specific *KRAS* Variant Analysis XXXV. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when **any** of the following criteria are met: A. The member has suspected or proven metastatic colorectal cancer B. The member is undergoing workup for metastasis of non-small cell lung cancer C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.	**Tumor Specific *KRAS* Variant Analysis** XXXV. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when **any** of the following criteria are met: A. The member has suspected or proven metastatic colorectal cancer B. The member is undergoing workup for metastasis of non-small cell lung cancer C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma.

Tumor Specific *MGMT* Methylation Analysis	**Tumor Specific *MGMT* Methylation Analysis**
XXXVI. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. High grade (stage III or IV) anaplastic oligodendroglioma 2. High grade (stage III or IV) anaplastic astrocytoma 3. High grade (stage III or IV) anaplastic glioma 4. High grade (stage III or IV) glioblastoma.	XXXVI. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. High grade (stage III or IV) anaplastic oligodendroglioma 2. High grade (stage III or IV) anaplastic astrocytoma 3. High grade (stage III or IV) anaplastic glioma 4. High grade (stage III or IV) glioblastoma.
Tumor Specific *MLH1* Methylation Analysis	**Tumor Specific *MLH1* Methylation Analysis**
XXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND** B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis.	XXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND** B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis.
Tumor Specific *MPL* Variant Analysis	**Tumor Specific *MPL* Variant Analysis**
XXVIII. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when: A. The member is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).	XXVIII. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when: A. The member is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia).
Tumor Specific Microsatellite Instability (MSI) Analysis	**Tumor Specific Microsatellite Instability (MSI) Analysis**
XXXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Colorectal cancer 2. Endometrial cancer 3. Gastric cancer 4. Esophageal and esophagogastric junction cancer 5. Recurrent, progressive or metastatic cervical carcinoma 6. Testicular cancer (nonseminoma) with progression after high dose chemotherapy or third-line therapy 7. Unresectable or metastatic gallbladder cancer	XXXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Colorectal cancer 2. Endometrial cancer 3. Gastric cancer 4. Esophageal and esophagogastric junction cancer 5. Recurrent, progressive or metastatic cervical carcinoma 6. Testicular cancer (nonseminoma) with progression after high dose chemotherapy or third-line therapy 7. Unresectable or metastatic gallbladder cancer

POLICY STATEMENT (No changes)	
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8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma 9. Unresectable or metastatic breast cancer 10. Small bowel adenocarcinom 11. Resectable, borderline resectable, or metastatic pancreatic cancer 12. Metastatic occult primary 13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva.	8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma 9. Unresectable or metastatic breast cancer 10. Small bowel adenocarcinom 11. Resectable, borderline resectable, or metastatic pancreatic cancer 12. Metastatic occult primary 13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva.
Tumor Specific *NPM1* Variant Analysis XL. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when: A. The member has cytogenetically normal acute myeloid leukemia (AML).	**Tumor Specific *NPM1* Variant Analysis** XL. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when: A. The member has cytogenetically normal acute myeloid leukemia (AML).
Tumor Specific *NRAS* Variant Analysis XLI. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when: A. The member has suspected or proven metastatic colorectal cancer.	**Tumor Specific *NRAS* Variant Analysis** XLI. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when: A. The member has suspected or proven metastatic colorectal cancer.
Tumor Specific *PIK3CA* Variant Analysis XLII. Tumor specific *PIK3CA* variant analysis (81309, 0155U) in solid tumors may be considered **medically necessary** when **either** of the following are met: A. The member has a diagnosis of recurrent or stage IV, HR positive, HER2 negative invasive breast cancer B. The member has a diagnosis of uterine rhabdomyosarcoma.	**Tumor Specific *PIK3CA* Variant Analysis** XLII. Tumor specific *PIK3CA* variant analysis (81309, 0155U) in solid tumors may be considered **medically necessary** when **either** of the following are met: A. The member has a diagnosis of recurrent or stage IV, HR positive, HER2 negative invasive breast cancer B. The member has a diagnosis of uterine rhabdomyosarcoma.
Tumor Specific *TP53* Variant Analysis XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when **either** of the following are met: A. The member has a diagnosis of **any** of the following:	**Tumor Specific *TP53* Variant Analysis** XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when **either** of the following are met: A. The member has a diagnosis of **any** of the following:

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1. Acute myeloid leukemia (AML) 2. Chronic lymphocytic leukemia (CLL) 3. Small lymphocytic leukemia (SLL) B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL).	1. Acute myeloid leukemia (AML) 2. Chronic lymphocytic leukemia (CLL) 3. Small lymphocytic leukemia (SLL) B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL).
Measurable (Minimal) Residual Disease (MRD) Analysis **Hematologic Minimal Residual Disease (MRD) Testing** XLIV. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Acute Lymphocytic Leukemia (ALL) 2. Multiple Myeloma 3. Chronic Lymphocytic Leukemia (CLL)	**Measurable (Minimal) Residual Disease (MRD) Analysis** **Hematologic Minimal Residual Disease (MRD) Testing** XLIV. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Acute Lymphocytic Leukemia (ALL) 2. Multiple Myeloma 3. Chronic Lymphocytic Leukemia (CLL)
Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing XLV. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue may be considered **medically necessary** when **all** of the following are met: A. The member has a personal history of metastatic colorectal or breast cancer, or muscle invasive bladder cancer B. The identification of recurrence or progression of disease will require a change in management C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, D. The member meets **one** of the following: 1. The member is currently being treated for cancer, **AND** a. The test has not previously been done for this episode of cancer 2. The member is not currently being treated for their cancer, **AND** a. The test has not been done in the past 12 months, **OR**	**Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing** XLV. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue may be considered **medically necessary** when **all** of the following are met: A. The member has a personal history of metastatic colorectal or breast cancer, or muscle invasive bladder cancer B. The identification of recurrence or progression of disease will require a change in management C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, D. The member meets **one** of the following: 1. The member is currently being treated for cancer, **AND** a. The test has not previously been done for this episode of cancer 2. The member is not currently being treated for their cancer, **AND** a. The test has not been done in the past 12 months, **OR**

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3. The member is being monitored for response to immune checkpoint inhibitor therapy, **AND** a. The test has not previously been ordered for this episode of cancer, **AND** b. The member has **either** of the following: i. Colorectal cancer, for which Guardant360 Response is being performed, **OR** ii. Any solid tumor, for which Signatera is being performed.	3. The member is being monitored for response to immune checkpoint inhibitor therapy, **AND** a. The test has not previously been ordered for this episode of cancer, **AND** b. The member has **either** of the following: i. Colorectal cancer, for which Guardant360 Response is being performed, **OR** ii. Any solid tumor, for which Signatera is being performed.
XLVI. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated.	XLVI. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated.
HPV-Related Solid Tumor Measurable (Minimal) Residual Disease (MRD) Testing	**HPV-Related Solid Tumor Measurable (Minimal) Residual Disease (MRD) Testing**
XLVII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers may be **medically necessary** when **all** of the following are met: A. The member has a personal history of HPV-driven oropharyngeal cancer B. The identification of recurrence or progression of disease will require a change in management C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, D. The member meets **one** of the following: 1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND** a. The test has not previously been done for this episode of cancer, **OR** 2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND** a. The test has not been done in the past 12 months.	XLVII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers may be **medically necessary** when **all** of the following are met: A. The member has a personal history of HPV-driven oropharyngeal cancer B. The identification of recurrence or progression of disease will require a change in management C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, D. The member meets **one** of the following: 1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND** a. The test has not previously been done for this episode of cancer, **OR** 2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND** a. The test has not been done in the past 12 months.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
XLVIII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers is considered **investigational** for all other indications. **Tumor Mutational Burden (TMB)** XLIX. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Recurrent or metastatic breast cancer 2. Unresectable or metastatic gallbladder cancer 3. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma 4. Suspected metastatic malignant occult primary tumor 5. Recurrent ovarian/fallopian tube/primary peritoneal cancer 6. Resectable or borderline resectable or metastatic or advanced pancreatic adenocarcinoma 7. Metastatic castration-resistant prostate cancer 8. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy 9. Endometrial carcinoma or uterine sarcoma 10. Locally advanced/metastatic ampullary adenocarcinoma 11. Metastatic chondrosarcoma 12. Metastatic chordoma 13. Widely metastatic Ewing sarcoma 14. Metastatic osteosarcoma 15. Metastatic esophageal or esophagogastric junction cancer 16. Gastric cancer 17. Metastatic salivary gland tumor 18. Adrenocortical carcinoma 19. Extrapulmonary poorly differentiated neuroendocrine carcinoma 20. Neuroendocrine large or small cell carcinoma	XLVIII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers is considered **investigational** for all other indications. **Tumor Mutational Burden (TMB)** XLIX. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when: A. The member has a diagnosis of **any** of the following: 1. Recurrent or metastatic breast cancer 2. Unresectable or metastatic gallbladder cancer 3. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma 4. Suspected metastatic malignant occult primary tumor 5. Recurrent ovarian/fallopian tube/primary peritoneal cancer 6. Resectable or borderline resectable or metastatic or advanced pancreatic adenocarcinoma 7. Metastatic castration-resistant prostate cancer 8. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy 9. Endometrial carcinoma or uterine sarcoma 10. Locally advanced/metastatic ampullary adenocarcinoma 11. Metastatic chondrosarcoma 12. Metastatic chordoma 13. Widely metastatic Ewing sarcoma 14. Metastatic osteosarcoma 15. Metastatic esophageal or esophagogastric junction cancer 16. Gastric cancer 17. Metastatic salivary gland tumor 18. Adrenocortical carcinoma 19. Extrapulmonary poorly differentiated neuroendocrine carcinoma 20. Neuroendocrine large or small cell carcinoma 21. Mixed neuroendocrine-non-neuroendocrine neoplasm

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21. Mixed neuroendocrine-non-neuroendocrine neoplasm 22. Structurally persistent/recurrent locoregional or distant metastatic papillary thyroid carcinoma 23. Structurally persistent/recurrent locoregional or distant metastatic follicular thyroid carcinoma 24. Structurally persistent/recurrent locoregional or distant metastatic oncocytic thyroid carcinoma 25. Stage IV anaplastic carcinoma 26. Vulvar squamous cell carcinoma 27. Metastatic small bowel adenocarcinoma.	22. Structurally persistent/recurrent locoregional or distant metastatic papillary thyroid carcinoma 23. Structurally persistent/recurrent locoregional or distant metastatic follicular thyroid carcinoma 24. Structurally persistent/recurrent locoregional or distant metastatic oncocytic thyroid carcinoma 25. Stage IV anaplastic carcinoma 26. Vulvar squamous cell carcinoma 27. Metastatic small bowel adenocarcinoma. 28.
Red Blood Cell Genotyping In Multiple Myeloma L. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of multiple myeloma B. The member is currently being treated or will be treated with Daratumumab (DARA).	**Red Blood Cell Genotyping In Multiple Myeloma** L. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of multiple myeloma B. The member is currently being treated or will be treated with Daratumumab (DARA).
Cancer Exome And Genome Sequencing LI. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0036U, 0297U, 81415, 81416, 81425, 81426) is considered **investigational**.	**Cancer Exome And Genome Sequencing** LI. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0036U, 0297U, 81415, 81416, 81425, 81426) is considered **investigational**.
Genetic Testing To Confirm The Identity Of Laboratory Specimens LII. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266, 81479), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance.	**Genetic Testing To Confirm The Identity Of Laboratory Specimens** LII. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266, 81479), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance.