BSC_CON_2.04	Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies		
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Section:	2.0 Medicine	**Page:**	Page 1 of 54

Example Test Table

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

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies		
Tissue based solid Tumor-Type Agnostic Molecular Profiling Panel Tests	FoundationOne CDx (Foundation Medicine)	0037U
	MSK-IMPACT (Memorial Sloan Kettering Medical Center)	0048U
	MI Cancer Seek - NGS Analysis (Caris Life Sciences)	0211U
	Oncotype MAP PanCancer Tissue Test (OncotypeDX)	0244U
	OmniSeq (Integrated Oncology)	81445, 81455
	OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs)	
	Tempus xT (Tempus)	
	Precise Tumor(Myriad)	
	Guardant360 TissueNext (Guardant)	0334U
	PGDx elio tissue complete (Personal Genome Diagnostics, Inc)	0250U
Stand-alone comprehensive RNA NGS testing	Oncology Fusion Gene Only NGS Panel (University of Minnesota Physicians Outreach Laboratory)	81456
Comprehensive or Large Panel Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81455
	Tempus xT Hematologic Malignancy (Tempus)	
	NeoTYPE Myeloid Disorders Profile (NeoGenomics Laboratories)	81450, 81451
	OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies (Mayo Clinic Laboratories)	
	Onkosight Myeloid Disorder Panel (BioReference Laboratories)	
	OmniSeq INSIGHT, Solid Tumor NGS Panel (DNA and RNA) (LabCorp Oncology)	
	Tempus xT with PD-L1 IHC, MMR IHC (Tempus)	
Tissue based Colorectal Cancer Focused Molecular Profiling Panels	PraxisTM Extended RAS Panel (Illumina)	0111U
	Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab)	81445
Lung Cancer Focused Molecular Profiling Panels	Oncomine Dx Target Test (NeoGenomics Laboratories)	0022U
	OnkoSight Advanced Comprehensive Lung (BioReference Laboratories)	81445

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Cutaneous Melanoma Focused Molecular Profiling Panels	Melanoma Panel (Knight Diagnostics)	81210, 81404
	OnkoSight Melanoma Panel (BioReference Laboratories)	81445
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML Gene Panel Assay (LabPMM, Invivoscribe Technologies)	0050U
	NeoTYPE AML Prognostic Profile (NeoGenomics)	81450
	LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics)	
Myeloproliferative Neoplasms (MPNs) Panel	Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories)	81219, 81270, 81339
	MPN, JAK2/MPL/CALR by NGS (BioReference Laboratories)	81219, 81270, 81279, 81338
Single Gene Testing of Solid Tumors and Hematologic Malignancies		
Tumor Specific BCR/ABL Kinase Domain Analysis	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170
	Onkosight NGS ABL1 Sequencing (BioReference Laboratories)	
Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis	BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics)	81206, 81207
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (LabCorp)	
	BCR/ABL1 (T(9;22)) RNA Quantitative with Interpretation (University of Iowa)	0016U
	MRDx BCR-ABL Test (MolecularMD)	0040U
Tumor Specific BRAF Variant Analysis	BRAF Mutation Analysis (NeoGenomics)	81210
Tumor Specific BRCA1/2 Variant Analysis	BRCA1 Mutation Analysis BRCA2 Mutation Analysis BRCA1/2 Mutation Analysis	81162, 81163, 81164, 81165, 81166, 81167, 81216
Tumor Specific CALR Variant Analysis	Calreticulin (CALR) Mutation Analysis (Quest Diagnostics)	81219
Tumor Specific CEBPA Variant Analysis	CEBPA Mutation Analysis (LabCorp)	81218
Tumor Specific EGFR Variant Analysis	EGFR Mutation Analysis (NeoGenomics Laboratories)	81235
Tumor Specific FLT3 Variant Analysis	FLT3 ITD and TKD Mutation Detection (ARUP Laboratories)	81245, 81246
	LeukoStrat CDx FLT3 Mutation Assay (Versiti)	0023U
	FLT3 ITD MRD by NGS (LABPMM, Invivoscribe Technologies)	0046U
Tumor Specific IDH1 and IDH2 Variant Analysis	IDH1/IDH2 Mutation Analysis (NeoGenomics)	81120, 81121
Tumor Specific IGHV Somatic Hypermutation Analysis	IgVH Mutation Analysis (NeoGenomics)	81263
Tumor Specific JAK2 Variant Analysis	JAK2 Exons 12 to 15 Sequencing (Mayo Clinic)	0027U
	JAK2 Mutation (University of Iowa)	0017U

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
	JAK2 V617F Mutation Analysis (Quest Diagnostics)	81270
Tumor Specific KIT Variant Analysis	KIT Mutation Analysis (ProPath)	81272
	KIT (D816V) Digital PCR (Labcorp)	81273
Tumor Specific KRAS Variant Analysis	KRAS Mutation Analysis (NeoGenomics)	81275, 81276, 81479
Tumor Specific MGMT Methylation Analysis	MGMT Promoter Methylation Assay (UCSF Molecular Diagnostics Laboratory)	81287
Tumor Specific MLH1 Methylation Analysis	MLH1 Promoter Methylation Analysis (NeoGenomics)	81288
Tumor Specific MPL Variant Analysis	MPL Mutation Analysis (MedFusion)	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 by NGS (LabPMM, Invivoscribe Technologies)	0049U
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)	81310
Tumor Specific NRAS Variant Analysis	NRAS Mutation Analysis (NeoGenomics)	81311, 81403, 81479
Tumor Specific PIK3CA Variant Analysis	PIK3CA Mutation Analysis (Quest Diagnostics)	81309
	PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp)	0155U
Tumor Specific RET Variant Analysis	RET Targeted Mutation Analysis RET Sequencing Analysis	81404, 81405, 81406
Tumor Specific TP53 Variant Analysis	TP53 MutationAnalysis (NeoGenomics)	81352, 81405
Measurable (Minimal) Residual Disease (MRD) Analysis		
Hematologic Minimal Residual Disease (MRD) Analysis	MyMRD NGS Panel,(LABPMM, Invivoscribe Technologies)	0171U
	ClonoSEQ (Adaptive Biotechnologies)	0364U
Solid Tumor Minimal Residual Disease (MRD) Analysis	Signatera - Residual Disease Test (MRD) - (Natera)	0340U
	PCM Tissue Profiling and MRD Baseline Assay (Invitae)	0306U
	PCM MRD Monitoring (Invitae)	0307U
	RaDaR (NeoGenomics)	81479
	Colvera (Clinical Genomics Pathology)	0229U
	MyMRD NGS Panel,(LABPMM, Invivoscribe Technologies)	0171U
Tumor Mutational Burden (TMB)		
Tumor Mutational Burden (TMB)	Tumor Mutational Burden (MedFusion)	81479
	Tumor Mutational Burden (Nebraska Medical Center - Molecular Diagnostic Laboratory)	
Red Blood Cell Genotyping in Multiple Myeloma		
Red Blood Cell Genotyping in Multiple	PreciseType HEA (Immucor)	0001U

Policy Statement Locations	Example Tests (Labs)	Common CPT Codes
Myeloma		
Cancer Exome and Genome Sequencing		
Cancer Exome/Genome Sequencing	Oncomap ExTra (Exact Sciences Laboratories)	0329U
	Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine)	81415, 81416, 81479
	Tempus xE (Tempus)	
Genetic Testing to Confirm the Identity of Laboratory Specimens		
Genetic Testing to Confirm the Identity of Laboratory Specimens	know error® DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC)	81265, 81266, 81479
	ToxProtect (Genotox Laboratories LTD)	0007U

Policy Statement

Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies
Tissue based solid Tumor-Type Agnostic Molecular Profiling Panel Tests

I. Tissue based comprehensive or smaller molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0244U, 0250U, 0334U81445, 81455) when Tumor Mutational Burden (TMB) results are included as part of the test may be considered **medically necessary** when the member meets **both** of the following criteria:
   A. Has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer
   B. Seeking further cancer treatment (e.g., therapeutic chemotherapy or immunotherapy [e.g., pembrolizumab/ Keytruda™), **OR** Had previous comprehensive solid tumor molecular profiling for a primary cancer diagnosis, and has a **different** stage III or IV primary cancer diagnosis for which this testing is being ordered.

II. Stand-alone comprehensive RNA NGS testing (81456) for more than 50 RNA specific fusions is considered **investigational** for all indications.

Tests including microsatellite instability (MSI), TMB, immunohistochemistry (IHC) and/or Cytogenetic Analyses should be billed using the appropriate CPT code for that inclusive panel test and the analysis should not be billed separately.

III. Duplicate analyses from the same tissue sample are considered **investigational**.

IV. The most aggressive or pooled tumor sample obtained should be sent for analysis. Multiple analyses from separate samples of the same tumor is considered **investigational**.

V. Tissue based comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0250U, 0334U 81445, 81455) are considered **investigational** for all other indications including but not limited to initial testing for stages I and II cancer.

VI. Simultaneous plasma (liquid biopsy) testing is considered **investigational** when tissue testing is also being requested.

Comprehensive or Large Panel Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

VII. Initial comprehensive or large panel molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when the member meets **any** of the following criteria:
- A. Has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML), or confirmed diagnosis of AML
- B. Has a newly diagnosed myelodysplastic syndrome
- C. Has persistent cytopenia(s) (at least 4-6 months) and a myelodysplastic syndrome is suspected **AND** other causes of cytopenia(s) have been ruled out, including but not limited to:
  1. Nutritional anemias (e.g., iron deficiency anemia, folate deficiency anemia, vitamin B12 deficiency anemia)
  2. Thyroid disease
  3. Drug-induced cytopenia
  4. Viral infection (e.g., HIV)
- D. Has suspected myeloproliferative neoplasm (a comprehensive panel can be ordered as part of initial evaluation, or after JAK2, CALR and MPL analysis were previously performed and the results were negative)
- E. Has a diagnosis of chronic myelogenous leukemia, **AND**
  1. BCR-ABL1 kinase domain mutation analysis has been performed and the results were negative, **OR**
  2. There has been progression to accelerated phase or blast phase.

VIII. Comprehensive or large panel 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 criteria are not intended to address liquid biopsies for solid tumors.

Tissue based Colorectal Cancer Focused Molecular Profiling Panels

IX. Tissue based somatic colorectal cancer focused molecular profiling panels (0111U, 81445) in solid tumors may be considered **medically necessary** when the member:
- A. Has suspected or proven metastatic, synchronous or metachronous colorectal cancer, **AND**
- B. Has **one** of the following:
  1. Not had previous somatic testing via a multigene cancer panel for the same primary diagnosis of colorectal cancer
  2. Has had previous somatic testing via a multigene cancer panel for a primary colorectal cancer diagnosis, and has a **new** primary colorectal cancer diagnosis for which this testing is being ordered

X. Tissue based colorectal cancer-focused molecular profiling panels (0111U, 81445) is considered **investigational** for all other indications.

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

Lung Cancer Focused Molecular Profiling Panels

XI. Somatic lung cancer focused molecular profiling panels (0022U, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria:
- A. A diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following:
  1. Lung adenocarcinoma

2. Large cell lung carcinoma
3. Squamous cell lung carcinoma
4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS)

B. Seeking further cancer treatment (e.g., therapeutic immunotherapy or chemotherapy)
C. Has **one** of the following:
   1. No previous somatic testing via a multigene cancer panel for the same primary lung cancer diagnosis
   2. With previous somatic testing via a multigene cancer panel for a primary lung cancer diagnosis, and has a **new** primary lung cancer diagnosis for which this testing is being ordered
   3. Repeat molecular profiling for solid tumors (0022U, 81445) when the member has progression while on targeted therapy for non-small cell lung cancer.

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

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

Cutaneous Melanoma Focused Molecular Profiling Panels

XIII. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria:
   A. Has a new diagnosis of stage IV melanoma or has recurrent melanoma
   B. Is seeking further cancer treatment (e.g. therapeutic chemotherapy)
   C. Has **one** of the following:
      1. No previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis
      2. With 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

XIV. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) are considered **investigational** for all other indications.

Note: If a panel is performed, appropriate panel codes should be used.
Algorithmic analysis/ gene expression tests are addressed in other policies.

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

XV. 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 the member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).

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

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

Myeloproliferative Neoplasms (MPNs) Panel Tests

XVII. Myeloproliferative neoplasm (MPN) molecular profiling panel (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) such as a serum erythropoietin level below the reference range for normal

B. A targeted (not comprehensive) panel including at a minimum *JAK2*, *CALR*, *MPL*. Note that *BCR/ABL1* can be included as a part of a panel or ordered separately when appropriate

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

Single-Gene Testing Of Solid Tumors And Hematologic Malignancies

Tumor Specific BCR/ABL Kinase Domain Analysis

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

Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis

XX. Tumor specific *BCR/ABL1* quantitation and breakpoint analysis (0016U, 0040U, 81206, 81207, 81208) in hematologic malignancies may be considered **medically necessary** when **either** of the following criteria is 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 workup for or to monitor disease progression of **any** of the following:
  1. Acute lymphoblastic leukemia (ALL)
  2. Acute myeloid leukemia (AML)
  3. Chronic myelogenous leukemia (CML)
  4. B-cell lymphoma

Tumor Specific *BRAF* Variant Analysis

XXI. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when the member:
- A. Has a diagnosis of **any** of the following:
  1. Suspected or proven metastatic, synchronous or metachronous colorectal cancer
  2. Advanced or metastatic non-small-cell lung cancer (NSCLC),
  3. Stage III or stage IV cutaneous melanoma
  4. Indeterminate thyroid nodules requiring biopsy
  5. Anaplastic thyroid carcinoma or locally recurrent advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma
  6. Low-grade glioma or pilocytic astrocytoma, **OR**
- B. Is being evaluated for Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype)

Tumor Specific *BRCA1/2* Variant Analysis

XXII. Somatic *BRCA1/2* variant analysis, (full sequence and duplication deletion 81162) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **either** of the following:
- A. Ovarian, fallopian tube and/or primary peritoneal cancer
- B. Metastatic prostate cancer

XXIII. Partial or serial analyses (81163, 81164, 81165, 81166, 81167, 81216) are considered **not medically necessary**.

Tumor Specific *CALR* Variant Analysis

XXIV. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when the member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.

Tumor Specific CEBPA Variant Tests

XXV. Tumor specific *CEBPA* variant analysis (81218) for hematologic malignancies may be considered **medically necessary** when the member has cytogenetically normal acute myeloid leukemia (AML).

Tumor Specific *EGFR* Variant Analysis

XXVI. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when the member has a diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following:

A. Lung adenocarcinoma
B. Large cell lung carcinoma
C. Squamous cell lung carcinoma
D. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS)

Tumor Specific *FLT3* Variant Analysis

XXVII. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) for hematologic malignancies may be considered **medically necessary** when the member meets **any** of the following criteria:

A. Has cytogenetically normal acute myeloid leukemia (AML)
B. Has a diagnosis of acute lymphocytic leukemia (ALL)
C. Has a diagnosis of myelodysplastic syndrome (MDS)

Tumor Specific *IDH1* and *IDH2* Variant Analysis

XXVIII. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of a glioma.

Tumor Specific IGHV Somatic Hypermutation Analysis

XXIX. Tumor specific *IGHV* somatic hypermutation analysis (81263) in hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of **any** of the following:

A. Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL)
B. Primary cutaneous B-cell lymphoma
C. Mantle cell lymphoma
D. Post-transplant lymphoproliferative disorder

Tumor Specific *JAK2* Variant Analysis

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

A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) such as a serum erythropoietin level below the reference range for normal
B. The member has acute lymphoblastic leukemia
C. The member is suspected to have a myelodysplastic syndrome

Tumor Specific *KIT* Targeted Variant Analysis

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

Tumor Specific KRAS Variant Analysis

XXXII. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria:
- A. Has suspected or proven metastatic, synchronous or unresectable metachronous colorectal cancer
- B. Is undergoing workup for metastatic non-small cell lung cancer
- C. When included in a panel approved for other indications

XXXIII. Somatic *KRAS* variant analysis (81275, 81276) in solid tumors is considered **investigational** in all other situations.

Tumor Specific *MGMT* Methylation Analysis

XXXIV. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when the member has a high grade glioma (stage III or IV), including **one** of the following:
- A. Anaplastic oligodendroglioma
- B. Anaplastic astrocytoma
- C. Anaplastic glioma
- D. Glioblastoma

Tumor Specific MLH1 Methylation Analysis

XXXV. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when the member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND** previous tumor testing showed loss of *MLH1* protein expression on immunohistochemistry (IHC) analysis.

Tumor Specific MPL Variant Analysis

XXXVI. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when the member displays clinical symptoms of a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.

Tumor Specific Microsatellite Instability (MSI) Analysis

XXXVII. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **any** of the following:
- A. Colorectal cancer
- B. Endometrial cancer
- C. Gastric cancer
- D. Pancreatic cancer
- E. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer
- F. Recurrent, progressive or metastatic cervical cancer
- G. Testicular cancer (nonseminoma) and has had progression after high dose chemotherapy or third-line therapy
- H. Unresectable or metastatic gallbladder cancer

I. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma
J. Unresectable or metastatic breast cancer
K. Small bowel adenocarcinoma
L. Metastatic occult primary

Tumor Specific NPM1 Variant Analysis

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

XXXIX. Genetic testing for FLT3 tyrosine kinase domain (FLT3-TKD) variants is considered **investigational**.

Tumor Specific NRAS Variant Analysis

XL. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when the member has suspected or proven metastatic, synchronous or metachronous colorectal cancer.

Tumor Specific PIK3CA Variant Analysis

XLI. Tumor specific *PIK3CA* variant analysis (81309, 0155U, 0177U) in solid tumors may be considered **medically necessary** when the member has **either** of the following:
A. Recurrent or stage IV, HR positive, HER2 negative invasive breast cancer
B. A diagnosis of uterine rhabdomyosarcoma.

Tumor Specific RET Variant Analysis

XLII. Tumor specific *RET* variant analysis (81404, 81405, 81406) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria:
A. A diagnosis of medullary thyroid cancer
B. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma
C. To predict treatment response (e.g., pralsetinib [Gavreto] or selpercatinib [Retevmo]) in patients with metastatic NSCLC

Tumor Specific TP53 Variant Analysis

XLIII. Tumor specific ***TP53*** variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when the member has **either** of the following:
A. A diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL)
B. Is undergoing diagnostic workup for mantle cell lymphoma (MCL)

Measurable (Minimal/ Molecular) Residual Disease (MRD) Analysis for Hematologic Neoplasms
Hematologic Minimal Residual Disease (MRD) Testing

XLIV. Measurable (minimal/ molecular) residual disease analysis (0171U, 81479) in bone marrow or peripheral blood for hematologic neoplasms may be **medically necessary** when the member has a diagnosis of **any** of the following:
A. Acute Lymphocytic Leukemia (ALL)
B. Multiple Myeloma
C. Chronic Lymphocytic Leukemia

Solid Tumor Minimal Residual Disease (MRD) Testing

XLV. Measurable (minimal) residual disease (MRD) analysis (0229U, 0340U, 0306U, 0307U, 81479) in solid tumor tissue is considered **investigational**.

Tumor Mutational Burden (TMB)

XLVI. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when the member has a diagnosis of **any** of the following:
- A. Recurrent or metastatic breast cancer
- B. Recurrent, progressive or metastatic cervical cancer
- C. Unresectable or metastatic gallbladder cancer
- D. Unresectable or metastatic extrahepatic cholangiocarcinoma
- E. Suspected metastatic malignant occult primary tumor
- F. Recurrent ovarian/fallopian tube/primary peritoneal cancer
- G. Metastatic or advanced pancreatic adenocarcinoma
- H. Metastatic castration-resistant prostate cancer
- I. Progression of testicular cancer (nonseminoma) after high dose or third line therapy
- J. Endometrial carcinoma or uterine sarcoma

Red Blood Cell Genotyping In Multiple Myeloma

XLVII. Red blood cell genotyping (0001U) in individuals with multiple myeloma may be considered **medically necessary** when the member has **both** of the following:
- A. A diagnosis of multiple myeloma
- B. Currently being treated or will be treated with Daratumumab (DARA)

Cancer Exome Sequencing

XLVIII. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0329U, 81415, 81416, 81425, 81426) is considered **investigational** unless part of another approved test.

Genetic Testing To Confirm The Identity Of Laboratory Specimens

XLIX. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266,), 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

Solid and hematologic tumors are typically addressed separately. Genetic tests can be further divided into tumor-specific and tumor-agnostic categories. The term may be easier to understand when looked at as "Solid Tumor (type agnostic)". Many treatments are now also considered to be tumor-agnostic in that they are effective based on the presence of a certain mutation rather than the type of cancer. The term "comprehensive" related to panel testing is poorly defined relative to how many genes are tested, for a single disorder or more general, application to tissue or liquid biopsy testing, inclusion of other tests (microsatellite instability or MSI, PDL-1, tumor mutational burden or TMB), etc. The term is not being used as much currently as a result. By comparison, there are smaller, more targeted panels, single markers (a single gene) and hotspot testing (may be multiple genes but only certain regions of those genes associated with known mutations).

Molecular profiling identifies specific molecules of DNA (deoxyribonucleic acid), RNA (ribonucleic acid), or proteins that are associated with a disorder. Molecular profiling can use various technologies to identify cancer biomarkers. Examples of molecular profiling technologies include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), next-generation sequencing (NGS) and quantitative polymerase chain reaction (qPCR). A cancer biomarker is a molecule associated with the presence of cancer in the body. A biomarker can be produced by the tumor itself, it may be a specific response by the body to the presence of cancer, or absent due to the tumor's effects. Biomarkers can be diagnostic, prognostic or predictive in nature. The findings can provide

information as to the probability that cancers will be sensitive or resistant to treatment (predictive). Targeted therapies are designed to be more effective for a specific tumor profile (a "profile" is information about the genes within cancer cells).

Stand-alone comprehensive RNA NGS testing (81456) for more than 50 RNA specific fusions is currently not supported by NCCN guidelines or other oncology guidelines. Cancer specific guidelines for RNA fusions are generally no more than 10 RNA fusion biomarkers.

Cytogenetic analyses focus on chromosomal rearrangements gains and losses and examine microscopically visible changes similar to what is done with routine karyotype analysis. See also FISH.

IHC uses fluorescent markers attached to antibodies that are added to a sample to see if they bond to specific antigens of interest.

FISH is similar to IHC but uses a fluorescent probe bound to targeted DNA sequences. When this probe is added to a sample it will bind to the specific areas of genes or chromosomes if present. FISH is typically higher resolution than standard cytogenetic analysis, but can be referred to as molecular cytogenetic testing.

NGS involves several technologies to establish the sequence of DNA or RNA. It can detect mutations, copy number variations (CNVs), or fusions.

qPCR is used to expand trace amounts of DNA to be better able to detect small amounts. It "amplifies" what is present in small quantities by repeatedly doubling the number of copies present.

Initial testing includes tumor testing (tumor block or FFPE slides from surgery or biopsy) and whole-blood testing (to allow matching of whole exome sequencing of tumor and blood DNA), and can take 35-42 days to complete. Subsequent monitoring testing is plasma only, based on initial testing results and is usually available within 7-14 days.

Criteria for Polycythemia Vera Testing

Based on the World Health Organization (WHO) major and minor criteria (see Table PG1), documentation of serum erythropoietin level below the reference range for normal meets a minor criterion for polycythemia vera. Serum erythropoietin testing may be done in place of JAK2 testing when the first four major criteria are met.

Diagnosis of PV: all major criteria, or first 4 major criteria plus the minor criterion.

Table PG1. WHO Diagnostic Criteria for Polycythemia Vera

Major Criteria
• Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women)
• Increased hematocrit (>49% in men or >48% in women)
• Other evidence of increased red cell volume
• Bone marrow biopsy showing hypercellularity for age with trilineage maturation, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
• *JAK2* V617F or *JAK2* exon 12 variant detected
Minor Criterion
• Serum erythropoietin level below the reference range for normal

Adapted from Arber et al (2016).
PV: polycythemia vera; WHO: World Health Organization.

Table PG2. Medically Necessary Tumor Testing By Cancer Type:

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Any solid tumor	Comprehensive molecular profiling panel for solid tumors	Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer
ALL	BCR-ABL1, TCF3-PBX1, ETV6-RUNX1, IL3-IGH, KMT2A, ABL2, CRLF2, CSF1R, EPOR, FLT3, IL7R, JAK1, JAK2, JAK3, PDGFRB, SH2B3, MRD	At diagnosis, or relapsed/refractory disease
AML	FISH, karyotype rearrangements: CBFB-MYH11, GAT2-MECOM, BCR-ABL, KMT2A-MLLT3, DEK-NUP214, RUNX1, RUNX1T1, ASXL1, KIT, NPM1, RUNX1, TP53, CEBPA, FLT3, IDH1, IDH2, Comprehensive molecular profiling panel	Workup
Ewing Sarcoma (bone cancer)	Translocations: ETV1, ETV4, EWSR1, FEV, FLI1, ERG, FUS,	Initial workup
Ewing Sarcoma (bone cancer)	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Progression after treatment
Breast Cancer	BRCA1, BRCA2, PD-L1, PIK3CA, NTRK1/2/3, MSI, MLH1, MSH2, MSH6, PMS2, TMB	Recurrent or metastatic
CNS Cancer Glioma-low grade	1p/19q, TERT promoter, H3F3A, HIST1H3B, BRAF, IDH1, IDH2, ATRX, MGMT Promoter Methylation	Pre-adjuvant therapy
CNS Cancer Medulloblastoma	APC, CTNNB1, GAB1, YAP1, TP53	Post-operative staging
Cervical Cancer	MLH1, MSH2, MSH6, PMS2, MSI, PD-L1, NTRK1/2/3, TMB,	Recurrent, progressive or metastatic disease
CLL/SLL	CCND1, 11:14 translocation, 11q:v translocation, CD19, CD200, CD5, FCER2, IGK, IGL, MME, MS4A1, CD247, CD3D, CD3E, CD3G, LEF1, ATM, CD38, IGH, ITGA4, ZAP70, TP53	Initial diagnosis
CML	BCR-ABL1, ABL1 Kinase Domain	Chronic phase adult CML
Colorectal Cancer	BRAF, KRAS, NRAS, HER2 amplifications (by NGS or IHC) MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC) if not previously done NTRK1/2/3, Comprehensive molecular profiling panel	Invasive, metastatic, synchronous (any T, any N, M1)
Colorectal Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Newly diagnosed
Cutaneous Melanoma	BRAF, KIT	Workup for metastatic or recurrent disease
Esophageal and EGJ Cancers	HER2, PD-L1, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Locally advanced, recurrent or metastatic adenocarcinoma
Gallbladder Cancer	MSI or MMR (MLH1, MSH2, MSH6 PMS2 by IHC) BRAF, ERBB2, FGFR2, IDH1, NTRK1/2/3, TMB	Unresectable or metastatic disease
Gastric Cancer	HER2, PD-L1, MSI if not previously done, NTRK1/2/3, Comprehensive molecular profiling panel	Locally advanced, recurrent or metastatic disease
Gastric Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC)	Workup
Hairy Cell Leukemia	CCND1, CD19, CD200, CD22, CD5, IL2RA, IL3RA, ITGAE, ITGAX, MME, MS4A21, BRAF, IGH	Initial diagnosis

Cancer Type	**Recommended Molecular Analysis** (see coverage criteria sections above)	**Timing of Analysis**
Hepatobiliary Cancers	MSI (PCR) or MMR (MLH1, MSH2, MSH6, PMS2 by IHC) TMB, BRAF, HER2, FGFR2, IDH1, NTRK1/2/3, RET	Unresectable or metastatic extrahepatic cholangiocarcinoma
Mantle Cell Lymphoma	TP53, CD19, CD5, FCER2, IGK, IGL, MME, MS4A1, BCL2, BCL6, CCND1, CD3E, CR2, MKI67, SOX11, IGH, CCND2 rearrangement, CCND3 rearrangement, CCND1	Initial diagnosis
Multiple Myeloma	MRD	Follow up/surveillance
Myelodysplastic Syndrome	ASXL1, BCOR, CALR, CBL, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2 Comprehensive hematologic malignancy panel testing	Initial evaluation
Myeloproliferative Neoplasms (polycythemia vera PV, essential thrombocythemia ET, myelofibrosis MF)	BCR-ABL, cytogenetics, FISH, Comprehensive molecular profiling panel For PV, ET, MF: JAK2, For ET, MF: MPL, CALR, ASXL1, EZH2, RAS	Diagnosis and prognostication
Non-small Cell Lung Cancer	EGFR, KRAS, MET, NTRK1/2/3, RET, ALK, ROS1, BRAF, PD-L1 (IHC), Comprehensive molecular profiling panel	Pre-adjuvant therapy, metastatic disease
B-Cell Lymphomas	IGH, IGK, IGL	Initial diagnosis
Occult Primary	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB, Comprehensive molecular profiling panel	Initial evaluation of suspected malignancy
Ovarian Cancer	BRCA1/2, homologous recombination deficiency, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), Comprehensive molecular profiling panel	Recurrent disease (if not previously done)
Pancreatic Adenocarcinoma	ALK, BRAF, BRCA1, BRCA2, ERBB2, FGFR2, KRAS, MLH1, MSH2, MSH6, NRG1, NTRK1, NTRK2, NTRK3, PALB2, PMS2, RET, ROS1 MSI and/or MMR (MLH1, MSH2, MSH6, PMS2)	Locally advanced or metastatic disease
Prostate Cancer	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L,	Metastatic disease
Prostate Cancer	MSI or MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB	Progressive metastatic disease
Testicular Cancer	MSI, MMR (MLH1, MSH2, MSH6, PMS2 by IHC), TMB	Recurrent disease
Thyroid Carcinoma (anaplastic carcinoma)	BRAF, ALK, RET, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2)	Initial workup
Thyroid Carcinoma (anaplastic, follicular, Hürthle cell, medullary, papillary carcinomas)	BRAF, ALK, RET, TMB, NTRK1/2/3 MSI or MMR (MLH1, MSH2, MSH6, PMS2)	Recurrence or metastatic disease
Uterine Neoplasms (endometrial carcinoma)	MMR (MLH1, MSH2, MSH6, PMS2 by IHC) TMB, NTRK1/2/3, POLE, TP53 expression Comprehensive genomic profiling panel	Diagnosis
Uterine Neoplasms (uterine sarcoma)	NTRK1/2/3, TMB, MSI	Metastatic or recurrent disease

Notes And Definitions

1. Tumor mutation burden testing is a measurement of **mutations** carried by **tumor** cells and is a predictive biomarker that is being studied to evaluate its association with response to immunotherapy.
2. Myeloproliferative Neoplasms are rare overlapping blood diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets.

   There are seven subcategories of myeloproliferative neoplasms:
   - Chronic myeloid leukemia (CML)
   - Polycythemia vera (PV)
   - Primary myelofibrosis (PMF)
   - Essential thrombocytopenia (ET)
   - Chronic neutrophilic leukemia
   - Chronic eosinophilic leukemia
   - Chronic eosinophilic leukemia-not otherwise specified
   - MPN, unclassifiable (MPN-U)
3. Advanced cancer is cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.

Clinical Considerations

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

NCCN and ASCO recommend that all individuals diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer have germline and somatic tumor testing (if not previously performed) for BRCA1 and BRCA2 mutations.

The genetic testing of tumors and hematologic malignancies (somatic mutation profiling) may reveal incidental germline findings or suspicion of a clinically significant germline mutation. Providers should communicate the potential for these incidental findings with their patients prior to somatic mutation profiling.

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

Description

The molecular analysis of solid tumors and hematologic malignancies aims to identify somatic oncogenic mutations in cancer. These mutations, often called “driver” mutations, are becoming increasingly useful for targeted therapy selection, and may give insight into prognosis and treatment response in a subset of cancers. In addition, molecular analysis of solid tumors and hematologic malignancies, in particular, can also aid in making a diagnosis of a specific type of malignancy. For solid tumors, molecular analysis can be performed via direct testing of the tumor (which is addressed in this policy) or via circulating tumor DNA or circulating tumor cells (CTCs) (see Other Related

Policies). For hematologic malignancies, molecular analysis can be performed on blood samples or bone marrow biopsy samples.

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

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

Related Policies

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

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

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

FDA:
Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

FoundationOne CDx (Foundation Medicine) initially received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) in 2017. It is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1. The approval is both tumor type and biomarker specific, and does not extend to all of the components included in the FoundationOne CDx product. The test is intended to identify patients who may benefit from treatment with targeted therapies in accordance with approved therapeutic product labeling. "Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms." FDA product code: PQP

In 2017, the Oncomine DX Target Test (Life Technologies Corp) received premarket approval by the FDA (P160045) to aid in selecting non-small cell lung cancer patients for treatment with approved targeted therapies. FDA product code: PQP

MSK-IMPACT (Memorial Sloan Kettering) received de novo marketing clearance in 2017 (DEN170058). "The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product." FDA product code: PZM

Subsequent marketing clearance through the FDA's 510(k) process (FDA product code PZM) include the following:

- Omics Core (NantHealth) received marketing clearance in 2019 (K190661). The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden.
- PGDx elio tissue complete (Personal Genome Diagnostics) received marketing clearance in 2020 (K192063). PGDx elio tissue complete is "intended to provide tumor mutation profiling information on somatic alterations (SNVs [single nucleotide variants], small insertions and deletions, one amplification and 4 translocations), microsatellite instability and tumor mutation burden (TMB)".
- The NYU Langone Genome PACT assay (NYU Langone Medical Center) is a 607-gene panel that received marketing clearance by the FDA in 2021 (K202304). The test assesses somatic point mutations, insertions and deletions smaller than 35 base pairs.

The intended use is by qualified health care professionals in accordance with professional guidelines for oncology, and not prescriptive for use of any specific therapeutic product.

OmniSeq Comprehensive® is approved by the New York State Clinical Laboratory Evaluation Program.

Table 1. Companion Diagnostic Indications for F1CDx

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Alunbrig® (brigatinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET	Tabrecta(™) (capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), or Perjeta® (pertuzumab)
	PIK3CA alterations	Piqray® (alpelsib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)
Cholangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq(™) (infigratinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene alterations	Lynparza® (olaparib)
Solid Tumors	Tumor mutational burden ≥10 mutations per megabase	Keytruda® (pembrolizumab)
	NTRK1/2/3 fusions	Vitrakvi® (larotrectinib)

Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Several laboratories offer these tests, including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM, and ARUP Laboratories, and they are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In May 2017, the FDA granted approval for midostaurin (Rydapt®, Novartis Pharmaceuticals). Rydapt® is a targeted therapy to be used in combination with chemotherapy when an *FLT3* variant is detected by the LeukoStrat® CDx *FLT3* Mutation Assay (Invivoscribe). In 2018, gilteritinib (Xospata®, Astellas Pharma US) was approved by the FDA for the treatment of relapsed or refractory acute myeloid leukemia (AML) with a *FLT3* mutation as detected by an FDA-approved test.

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical

Laboratory Improvement Amendments. More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2*, *CALR*, and *MPL* testing under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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).

Rationale

Solid Tumor-Type Agnostic Molecular Profiling Panel Tests
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on breast cancer (4.2022) 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 (2.2023) 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 (6.2022) recommends molecular testing for advanced or metastatic disease, including *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3*, *MET*ex14 skipping, *RET, PD-L1*. They also recommend broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available. (p. NSCL-18). The guidelines also state that 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. (p. NSCL-H 6 of 7)
The NCCN guideline for colon cancer (2.2022) 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 (2.2022) recommends that patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering trastuzumab therapy have IHC for *HER2* and NGS when limited diagnostic tissue is available or patient can't undergo a traditional biopsy. 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 3 of 6).

The NCCN guideline for ovarian cancer including Fallopian tumor cancer and primary peritoneal cancer (5.2022) recommends that patients with recurrent disease, tumor molecular analysis have at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor specific or tumor-agnostic benefit. (p OV-6) More comprehensive testing may be particularly important in less common histologies with limited approved therapeutic options. (p. OV-B 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 (1.2022) recommends tumor/somatic molecular profiling for patients with local advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. They also recommend considering specifically testing for

potentially actionable somatic findings including but not limited to fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations *BRAF, BRCA1/2*, *KRAS*, *PALB2*, amplifications (*HER2*), MSI, and or mismatch repair deficiency. (p. PANC-1A)

The NCCN guideline for prostate cancer (1.2023) recommends for somatic tumor testing and that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. 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)

Comprehensive Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for acute myeloid leukemia (2.2022) recommends for patients over the age of 18 testing that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses. (p.EVAL-1). Multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment (p. EVAL-1A). The NCCN guidelines for myelodysplastic syndromes (1.2023) recommend that patients who have persistent cytopenia (at least 4-6 months) and lack other underlying conditions that could cause cytopenia should be evaluated for myelodysplastic syndromes. (p. MS-3) NCCN describes cytopenia that is suspicious for myelodysplasia as the presence of peripheral blood dysplasia, blasts, or MDS-associated cytogenetic abnormalities. They say cytopenias are defined as values lower than standard lab hematologic levels, being cognizant of age, sex, ethnic, and altitude norms (p. MDS-1, p. MDS-2). NCCN recommends ruling out other causes of anemia, such as nutritional deficiency of folate and vitamin B12, as well as measuring thyroid stimulating hormone levels, and HIV testing if clinically indicated (p. MDS-1).

The NCCN guidelines for myeloproliferative neoplasms (3.2022) recommend for patients suspected of having an MPN to have molecular testing for *JAK2* V617F*, CALR* and *MPL* mutations for patient with symptoms of essential thrombocythemia or myelofibrosis, and *JAK2* exon 12 mutations for patients with polycythemia vera. This testing can be done in a stepwise manner, or as an NGS multigene panel (p. MPN-1).

The NCCN guidelines for chronic myeloid leukemia (1.2023) indicate that a patient with advanced phase CML in either accelerated or blast phase should consider mutational analysis with a myeloid mutation panel (CML-1). Patients on TKI therapy who have progressed to accelerated or blast phase should consider a myeloid mutation panel to identify *BCR-ABL-1*-independent resistance mutations in patients with no BCR-ABL 1 kinase domain mutations (p. CML-E).

Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on occult primary (2.2023) recommends MSI and MMR testing as part of the initial work up for patients with cancer of unknown primary. (p. OCC-1) The guideline further recommends consideration of NGS to identify actionable genomic aberrations in individuals with localized adenocarcinoma or carcinoma not otherwise specified. (p. OCC-2)

The NCCN guideline on non-small cell lung cancer (6.2022) recommends molecular testing for advanced or metastatic disease, including *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET*ex14 skipping, *RET, PD-L1*. They also recommend broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available. (p. NSCL-18)

The NCCN guideline for colon cancer (2.2022) recommends all patients with metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-B 4 of 8)

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

The NCCN guideline for ovarian cancer including Fallopian tube cancer and primary peritoneal cancer (5.2022) recommends that patients with recurrent disease, tumor molecular analysis have at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor specific or tumor-agnostic benefit. (p OV-6) More comprehensive testing may be particularly important in less common histologies with limited approved therapeutic options. (p. OV-B 1 of 3)

The NCCN guideline for pancreatic adenocarcinoma (1.2022) recommends tumor/somatic molecular profiling for patients with local advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. They also recommend considering specifically testing for potentially actionable somatic findings including but not limited to fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations *BRAF, BRCA1/2, KRAS, PALB2*, amplifications (*HER2*), MSI, and or mismatch repair deficiency. (p. PANC-1A)

The NCCN guideline for prostate cancer (1.2023) recommends for somatic tumor testing and that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. They also recommend tumor testing for alterations in homologous recombination DNA report genes such as *BRCA1/2, ATM, PALB2, FANCA, RAD512D, CHEK2, CDK12*, is for patients with metastatic prostate cancer. (p. PROS-C 3 of 3)

Colorectal Cancer Focused Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guideline for colon cancer (2.2022) recommends all patients with metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-B 4 of 8).

Lung Cancer Focused Molecular Profiling Panels
National Comprehensive Cancer Network (NCCN)
The NCCN guideline for non-small cell lung cancer (6.2022) 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 (3.2022) recommend *BRAF* and *KIT* testing, but broader genomic profiling (such as larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial (p. ME-C 4 of 8).

Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panel
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for acute myeloid leukemia (2.2022) recommends for patients over the age of 18 testing that includes a complete blood count, platelets, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, vitamin B12 and folic acid, prothrombin time, partial thromboplastin time, fibrinogen, and bone marrow core biopsy and aspirate analyses. (p.EVAL-1). Multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment (p. EVAL-1A).

Myeloproliferative Neoplasms (MPNs) Panel
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on myeloproliferative neoplasms (3.2022) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts is recommended to exclude the diagnosis of CML. Additionally, they recommend that molecular testing for *JAK2* mutations is recommended in initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MPN-1)

Tumor Specific *BCR/ABL* Kinase Domain Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on chronic myeloid leukemia (1.2023) outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, including *BCR/ABL1* tests for diagnosis, monitoring, and *ABL* kinase domain single nucleotide variants. *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 (1.2022) recommend somatic genetic testing for all patients with ALL, as Ph-like ALL has a phenotype associated with recurrent gene fusions/mutations which may guide TKI treatment decision-making. (p. ALL-1 and ALL-1A) Similar recommendations are made in the NCCN guidelines for pediatric acute lymphoblastic leukemia (1.2022). (p. PEDALL-1 and PEDALL-1A)

Tumor Specific *BCR/ABL* Quantitation and Breakpoint Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on pediatric acute lymphocytic leukemia (1.2022) recommend that the presence of recurrent genetic abnormalities, specifically *BCR-ABL1* and *ETV6-RUNX1,* should be evaluated using karyotyping, FISH, or RT-PCR. They further recommend that if testing for those recurrent genetic abnormalities is negative, additional testing for recurrent genetic abnormalities is encouraged in some patients and may aid in risk stratification. (p. PEDALL-1 and PEDALL-1A)
The NCCN guidelines on acute lymphocytic leukemia (1.2022) recommend that the presence of recurrent genetic abnormalities, specifically *BCR-ABL1*, should be evaluated using karyotyping, FISH, or RT-PCR. They further recommend that if testing for *BCR-ABL1* is negative, additional testing for recurrent genetic abnormalities associated with Ph-like ALL is essential. (p. ALL-1 and ALL-1A)
The NCCN guidelines on B-cell lymphomas (5.2022) include molecular testing for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphoblastic lymphoma. (p. BLAST-1).
The NCCN guidelines for myeloproliferative neoplasms (3.2022) recommend evaluation for *BCR-ABL1* to exclude a diagnosis of CML. (p. MPN-1)

The NCCN guidelines of acute myeloid leukemia (2.2022) recommend BCR-ABL1 testing to assist in risk stratification of AML. (p. AML-A 1 of 4)

The NCCN guidelines for chronic myeloid leukemia (1.2023) 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 (3.2022) 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 (1.2023) 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 (3.2022) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. (ME-C 4 of 8) The NCCN guideline on Central Nervous System Cancers (2.2022) 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 (6.2022) 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 (2.2022) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic synchronous adenocarcinoma. (p. COL-4)

Tumor Specific *BRCA1/2* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guideline on epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer (5.2022) recommends that all patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should have genetic risk evaluation and germline and somatic testing of *BRCA1* and *BRCA2* if not previously done. (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 (1.2023) 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)

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)

- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results. (Recommendation 1.2, p. 6)
- Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer. (Recommendation 1.4, p. 6)
- First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing. (Recommendation 1.5, p. 6)
- Clinical decision making should not be made based on a variant of uncertain significance. (p. 2)
- Women with epithelial ovarian cancer should have testing at the time of diagnosis. (p. 2)

Tumor Specific *CALR* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on myeloproliferative neoplasms (3.2022) recommend 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)

Tumor Specific *CEBPA* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on acute myeloid leukemia (2.2022) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *EGFR* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on Non-Small Cell Lung Cancer (6.2022) state that molecular testing for *EGFR* mutations should be performed when adjuvant TKI therapy is a consideration for NSCLC stage IB–IIIA. 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 *FLT3* Variant Analysis
National Comprehensive Cancer Network (NCCN)
The NCCN guidelines on acute myeloid leukemia (2.2022) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *IDH1* and *IDH2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (2.2022) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications, including *IDH1/IDH2*.. (p. EVAL-1)

The NCCN guideline on Central Nervous System Cancers (2.2022) 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

The NCCN chronic lymphocytic leukemia/small lymphocytic lymphoma guidelines (1.2023) 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 (5.2022) 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 B-cell lymphomas guidelines (2.2022) 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 (3.2022) recommend that FISH or RT-PCR to detect *BCR-ABL1* transcripts to exclude the diagnosis of CML (p. MS-6). Additionally, they recommend molecular testing for *JAK2* mutations in the initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. The guidelines also state that NGS may also be useful to establish the clonality in certain circumstances and may identify second, third and fourth mutations that may hold prognostic relevance. (p. MS-7)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (1.2022) 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 (1.2023) 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 (3.2022) recommends *BRAF* mutation testing in patients with stage III cutaneous melanoma at high risk for recurrence. Additionally, the panel strongly encourages testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. They further recommend that if feasible, broader genomic profiling with NGS panels be performed in individuals with stage IV or recurrent melanoma especially if the test results could guide future treatment options. (p. ME-C, 4 of 8)

Current NCCN guidelines for gastrointestinal stromal tumors (2.2022) 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 (2.2022) 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 (2.2022) 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 (2.2022) 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. Version (6.2022) 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)*

American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and Association for Molecular Pathology (AMP)

ASCO, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology (2017) published the following recommendations for the use of molecular biomarkers for the evaluation of colorectal cancer:

- Patients with CRC considered for anti-*EGFR* therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4. (p. 193)
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification (p. 201)
- *BRAF* p.V600 mutational analysis should be performed in dMMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome. (p. 201)
- Clinicians should order MMR status testing in patients with CRCs for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. (p. 192)

- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors. (p. 192)

Tumor Specific *MGMT* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Central Nervous System Cancers (2.2022) recommends molecular testing of glioblastoma, because if a driver mutation (such as *BRAF* V600E-activating mutations, or *NTRK*

fusions) is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial. Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection. The panel also recommends *IDH* mutation testing in patients with glioma. (p. BRAIN-F, 2 of 10)

Tumor Specific *MLH1* Methylation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Genetic/Familial High-Risk Assessment: Colorectal (1.2022) 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 (3.2022) 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 (2.2022) 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 (1.2022) recommend MSI (among other studies) for patients with endometrial carcinoma. (p. ENDO-A 2 of 4)

The NCCN guideline on gastric cancer (2.2022) recommends MSI testing for all newly diagnosed gastric cancers. (p. GAST-1)

The NCCN guideline on esophageal and esophagogastric junction cancer (5.2022) recommends MSI by PCR or NGS for patients with locally advanced, recurrent, or metastatic esophageal and EGJ cancers. (p. ESOPH-B 4 of 6)

The NCCN guidelines for cervical cancer (1.2022) recommend MSI testing for patients with progressive, recurrent, or metastatic disease. (p. CERV-A 1 of 3)

The NCCN guideline for testicular cancer (2.2022) 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 hepatobiliary cancers (3.2022) 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 (4.2022) 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 (2.2022) recommend universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma. (p. SBA-B)

The NCCN guidelines for an occult primary (2.2023) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology. (p. OCC-1)

Tumor Specific *NPM1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (2.2022) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

Tumor Specific *NRAS* Variant Analysis

American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and Association for Molecular Pathology (AMP)

ASCO, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology (2017) published the following recommendations for the use of molecular biomarkers for the evaluation of colorectal cancer:

- Patients with CRC considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4. (p.193)
- *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification. (p. 201)
- *BRAF* p.V600 mutational analysis should be performed in dMMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome. (p. 201)
- Clinicians should order MMR status testing in patients with CRCs for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. (p. 192)
- There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors. (p. 192)

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on colon cancer (2.2022) 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 (4.2022) recommends that recurrent or stage IV HR-positive/HER2-negative breast cancers be assessed for *PIK3CA* mutations with tumor or liquid biopsy to identify candidates for Alpelisib + fulvestrant. They also recommend that recurrent or stage IV MSH-H/dMMR breast cancers that have progressed following prior treatment be considered for treatment with Pembrolizumab. (p. BINV-R 1 of 3)

The NCCN guidelines on uterine cancer (1.2022) recommend for Rhabdomyosarcoma, *DICER1* mutations are present in up to 95% of embryonal RMS. *PIK3CA* and *TP53* mutations in pleomorphic tumors. And *FOXO1* fusion in alveolar tumors. (p. UTSARC-A 7 of 8)

Tumor Specific *RET* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on thyroid carcinoma (3.2022) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS and somatic *RET* testing in all individuals with newly diagnosed medullary thyroid carcinoma. Additionally they comment that molecular testing has shown to be beneficial when making targeted therapy decisions. (p. THYR-B) 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-3)

Tumor Specific *TP53* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on acute myeloid leukemia (2.2022) state that a variety of gene mutations are associated with specific prognoses and may guide medical decision making while other mutations may have therapeutic implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. Additionally, they recommend that *ASXL1, BCR-ABL1* and *PML-RAR* alpha be tested in all patients and further recommend that multiplex gene panels and NGS analysis be used for a comprehensive prognostic assessment. (p. MS-3)

The NCCN guidelines on B-cell lymphoma (5.2022) recommend *TP53* mutation analysis for patients with a diagnosis of mantle cell lymphoma in order to direct treatment selection, as patients with a *TP53* mutation have been associated with poor prognosis when treated with conventional therapy. (p. MANT-1)

The NCCN guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (1.2022) recommend *TP53* sequencing analysis and *IGHV* mutation analysis to inform prognosis and therapeutic options for patients diagnosed with CLL/SLL or upon progression or recurrence (p. CSLL-1). Minimal residual disease testing at the end of treatment for CLL is recommended. (p. CSLL-2, 2 of 2)

Measurable (Minimal) Residual Disease (MRD) Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for acute lymphoblastic leukemia (1.2022) recommend baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis (p. ALL-1). After treatment induction, MRD is recommended to determine consolidation therapy (p. ALL-3). For surveillance on bone marrow aspirate, MRD assessment is recommended (p. ALL-6).

The NCCN guidelines for multiple myeloma (2.2023) 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 (3.2022) recommend minimal residual disease testing at the end of treatment for CLL/SLL. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method (p. CSLL-E 1 of 2).

Tumor Mutational Burden (TMB)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for breast cancer (4.2022) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. BINV-R 1 of 3)
The NCCN guidelines for cervical cancer (1.2022) recommend consideration of tumor mutation burden testing for patients for whom pembrolizumab is being considered for treatment. (p. CERV-F 1 of 3)

The NCCN guidelines for hepatobiliary cancers (3.2022) 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 (2.2023) 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/Fallopian tube cancer/primary peritoneal cancer (5.2022) 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 (1.2022) recommend testing tumor mutational burden for patients with locally advanced and metastatic pancreatic cancer as pembrolizumab may be considered for treatment. (p. PANC-F 6 of 9)

The NCCN guideline for prostate cancer (1.2023) 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 (2.2022) 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 (1.2022) 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)

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 July 2022) recommending that all patients should undergo baseline phenotype and genotype prior to initiation of anti-CD38 monoclonal antibody treatment (daratumumab) to mitigate the potential of anti-CD38 interference with serologic testing. The bulletin also notes that this genotyping can be performed after the initiation of treatment. (p. 2 and 3)

Cancer Exome and Genome Sequencing

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

Genetic Testing to Confirm the Identity of Laboratory Specimens

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

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Current diagnoses and status (i.e., type of cancer, stage)
  - Family history, if applicable
  - Reason for test when applicable
  - Pertinent past procedural and surgical history (i.e., biopsies, resections, etc.)
  - Pertinent past genetic or other laboratory tests as applicable (i.e., somatic/tumor or germline test results including but not limited to HER2, PD-L1, MSI, BRCA, etc.; serum erythropoietin level; cytogenetic analysis, etc.)

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

- Results/reports of tests performed
- Procedure report(s)

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 ***(Code revision effective 4/1/2023)***
	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

Type	Code	Description
	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], 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
	0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status (PLA code for the therascreen® PIK3CA RGQ PCR Kit test from QIAGEN)
	0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis
	0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue
	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

Type	Code	Description
	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 ***(Code effective 4/1/2023)***
	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, gene rearrangements, microsatellite instability, and tumor mutational burden ***(Code effective 4/1/2023)***
	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 ***(Code effective 7/1/2023)***
	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 ***(Code effective 10/1/2023)***
	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 ***(Code effective 1/1/2024)***
	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)
	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

Type	Code	Description
	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
	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)

Type	Code	Description
	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
	81304	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
	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)
	81403	Molecular Pathology Procedure Level 4
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	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
	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,

Type	Code	Description
		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.

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:** **Tissue based solid Tumor-Type Agnostic Molecular Profiling Panel Tests** I. **Tissue based** comprehensive or smaller molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0244U, 0250U, 0334U81445, 81455) when Tumor Mutational Burden (TMB) results are included as part of the test may be considered **medically necessary** when the member meets **both** of the following criteria: A. Has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer B. Seeking further cancer treatment (e.g., therapeutic chemotherapy or immunotherapy [e.g., pembrolizumab/ Keytruda™), **OR** Had previous comprehensive solid tumor molecular profiling for a primary cancer diagnosis, and has a **different** stage III or IV primary cancer diagnosis for which this testing is being ordered. II. Stand-alone comprehensive RNA NGS testing (81456) for more than 50 RNA specific fusions is considered **investigational** for all indications. Tests including microsatellite instability (MSI), TMB, immunohistochemistry (IHC) and/or Cytogenetic Analyses should be billed using the appropriate CPT code for that inclusive panel test and the analysis should not be billed separately. III. Duplicate analyses from the same tissue sample are considered **investigational**.	**Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies BSC_CON_2.04** **Policy Statement:** **Tissue based solid Tumor-Type Agnostic Molecular Profiling Panel Tests** I. **Tissue based** comprehensive or smaller molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0244U, 0250U, 0334U81445, 81455) when Tumor Mutational Burden (TMB) results are included as part of the test may be considered **medically necessary** when the member meets **both** of the following criteria: A. Has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer B. Seeking further cancer treatment (e.g., therapeutic chemotherapy or immunotherapy [e.g., pembrolizumab/ Keytruda™), **OR** Had previous comprehensive solid tumor molecular profiling for a primary cancer diagnosis, and has a **different** stage III or IV primary cancer diagnosis for which this testing is being ordered. II. Stand-alone comprehensive RNA NGS testing (81456) for more than 50 RNA specific fusions is considered **investigational** for all indications. Tests including microsatellite instability (MSI), TMB, immunohistochemistry (IHC) and/or Cytogenetic Analyses should be billed using the appropriate CPT code for that inclusive panel test and the analysis should not be billed separately. III. Duplicate analyses from the same tissue sample are considered **investigational**.

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IV. The most aggressive or pooled tumor sample obtained should be sent for analysis. Multiple analyses from separate samples of the same tumor is considered **investigational**.	IV. The most aggressive or pooled tumor sample obtained should be sent for analysis. Multiple analyses from separate samples of the same tumor is considered **investigational**.
V. Tissue based comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0250U, 0334U, 81445, 81455) are considered **investigational** for all other indications including but not limited to initial testing for stages I and II cancer.	V. Tissue based comprehensive molecular profiling panels for solid tumors (0037U, 0048U, 0211U, 0250U, 0334U, 81445, 81455) are considered **investigational** for all other indications including but not limited to initial testing for stages I and II cancer.
VI. Simultaneous plasma (liquid biopsy) testing is considered **investigational** when tissue testing is also being requested.	VI. Simultaneous plasma (liquid biopsy) testing is considered **investigational** when tissue testing is also being requested.
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Comprehensive or Large Panel Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels	**Comprehensive or Large Panel Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels**
VII. Initial comprehensive or large panel molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML), or confirmed diagnosis of AML B. Has a newly diagnosed myelodysplastic syndrome C. Has persistent cytopenia(s) (at least 4-6 months) and a myelodysplastic syndrome is suspected **AND** other causes of cytopenia(s) have been ruled out, including but not limited to: 1. Nutritional anemias (e.g., iron deficiency anemia, folate deficiency anemia, vitamin B12 deficiency anemia) 2. Thyroid disease 3. Drug-induced cytopenia 4. Viral infection (e.g., HIV) D. Has suspected myeloproliferative neoplasm (a comprehensive panel can be ordered as part of initial	VII. Initial comprehensive or large panel molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML), or confirmed diagnosis of AML B. Has a newly diagnosed myelodysplastic syndrome C. Has persistent cytopenia(s) (at least 4-6 months) and a myelodysplastic syndrome is suspected **AND** other causes of cytopenia(s) have been ruled out, including but not limited to: 1. Nutritional anemias (e.g., iron deficiency anemia, folate deficiency anemia, vitamin B12 deficiency anemia) 2. Thyroid disease 3. Drug-induced cytopenia 4. Viral infection (e.g., HIV) D. Has suspected myeloproliferative neoplasm (a comprehensive panel can be ordered as part of initial evaluation, or after JAK2, CALR and MPL analysis were previously performed and the results were negative)

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evaluation, or after JAK2, CALR and MPL analysis were previously performed and the results were negative) E. Has a diagnosis of chronic myelogenous leukemia, **AND** 1. BCR-ABL1 kinase domain mutation analysis has been performed and the results were negative, **OR** 2. There has been progression to accelerated phase or blast phase.	E. Has a diagnosis of chronic myelogenous leukemia, **AND** 1. BCR-ABL1 kinase domain mutation analysis has been performed and the results were negative, **OR** 2. There has been progression to accelerated phase or blast phase.
VIII. Comprehensive or large panel 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.	VIII. Comprehensive or large panel 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 criteria are not intended to address liquid biopsies for solid tumors.	**Note:** If a multigene panel is performed, appropriate panel codes should be used. These criteria are not intended to address liquid biopsies for solid tumors.
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Tissue based Colorectal Cancer Focused Molecular Profiling Panels IX. Tissue based somatic colorectal cancer focused molecular profiling panels (0111U, 81445) in solid tumors may be considered **medically necessary** when the member: A. Has suspected or proven metastatic, synchronous or metachronous colorectal cancer, **AND** B. Has **one** of the following: 1. Not had previous somatic testing via a multigene cancer panel for the same primary diagnosis of colorectal cancer 2. Has had previous somatic testing via a multigene cancer panel for a primary colorectal cancer diagnosis, and has a **new** primary colorectal cancer diagnosis for which this testing is being ordered	**Tissue based Colorectal Cancer Focused Molecular Profiling Panels** IX. Tissue based somatic colorectal cancer focused molecular profiling panels (0111U, 81445) in solid tumors may be considered **medically necessary** when the member: A. Has suspected or proven metastatic, synchronous or metachronous colorectal cancer, **AND** B. Has **one** of the following: 1. Not had previous somatic testing via a multigene cancer panel for the same primary diagnosis of colorectal cancer 2. Has had previous somatic testing via a multigene cancer panel for a primary colorectal cancer diagnosis, and has a **new** primary colorectal cancer diagnosis for which this testing is being ordered

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X. Tissue based colorectal cancer-focused molecular profiling panels (0111U, 81445) is considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. back to top **Lung Cancer Focused Molecular Profiling Panels** XI. Somatic lung cancer focused molecular profiling panels (0022U, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria: A. A diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following: 1. Lung adenocarcinoma 2. Large cell lung carcinoma 3. Squamous cell lung carcinoma 4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS) B. Seeking further cancer treatment (e.g., therapeutic immunotherapy or chemotherapy) C. Has **one** of the following: 1. No previous somatic testing via a multigene cancer panel for the same primary lung cancer diagnosis 2. With previous somatic testing via a multigene cancer panel for a primary lung cancer diagnosis, and has a **new** primary lung cancer diagnosis for which this testing is being ordered 3. Repeat molecular profiling for solid tumors (0022U, 81445) when the member has progression while on targeted therapy for non-small cell lung cancer. XII. Lung cancer-focused molecular profiling panels (0022U, 81445) is considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used.	X. Tissue based colorectal cancer-focused molecular profiling panels (0111U, 81445) is considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. back to top **Lung Cancer Focused Molecular Profiling Panels** XI. Somatic lung cancer focused molecular profiling panels (0022U, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria: A. A diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following: 1. Lung adenocarcinoma 2. Large cell lung carcinoma 3. Squamous cell lung carcinoma 4. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS) B. Seeking further cancer treatment (e.g., therapeutic immunotherapy or chemotherapy) C. Has **one** of the following: 1. No previous somatic testing via a multigene cancer panel for the same primary lung cancer diagnosis 2. With previous somatic testing via a multigene cancer panel for a primary lung cancer diagnosis, and has a **new** primary lung cancer diagnosis for which this testing is being ordered 3. Repeat molecular profiling for solid tumors (0022U, 81445) when the member has progression while on targeted therapy for non-small cell lung cancer. XII. Lung cancer-focused molecular profiling panels (0022U, 81445) is considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used.

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Cutaneous Melanoma Focused Molecular Profiling Panels XIII. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria: A. Has a new diagnosis of stage IV melanoma or has recurrent melanoma B. Is seeking further cancer treatment (e.g. therapeutic chemotherapy) C. Has **one** of the following: 1. No previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis 2. With 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 XIV. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) are considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. Algorithmic analysis/ gene expression tests are addressed in other policies. **Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels** XV. 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 the member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML). XVI. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) is considered **investigational** for all other indications.	**Cutaneous Melanoma Focused Molecular Profiling Panels** XIII. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) may be considered **medically necessary** when the member meets **all** of the following criteria: A. Has a new diagnosis of stage IV melanoma or has recurrent melanoma B. Is seeking further cancer treatment (e.g. therapeutic chemotherapy) C. Has **one** of the following: 1. No previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis 2. With 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 XIV. Cutaneous melanoma focused molecular profiling panels (81210, 81404, 81445) are considered **investigational** for all other indications. **Note:** If a panel is performed, appropriate panel codes should be used. Algorithmic analysis/ gene expression tests are addressed in other policies. **Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels** XV. 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 the member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML). XVI. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) is considered **investigational** for all other indications.

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Note: If a multigene panel is performed, appropriate panel codes should be used. back to top **Myeloproliferative Neoplasms (MPNs) Panel Tests** XVII. Myeloproliferative neoplasm (MPN) molecular profiling panel (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) such as a serum erythropoietin level below the reference range for normal B. A targeted (not comprehensive) panel including at a minimum *JAK2*, *CALR*, *MPL*. Note that *BCR/ABL1* can be included as a part of a panel or ordered separately when appropriate XVIII. Myeloproliferative neoplasm (MPN) molecular profiling panel (81219, 81270, 81279, 81338, 81339) analysis is considered **investigational** for all other indications. back to top **Single-Gene Testing Of Solid Tumors And Hematologic Malignancies** **Tumor Specific BCR/ABL Kinase Domain Analysis** XIX. 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. **Any** of the following: 1. Initial response to TKI therapy is inadequate 2. Loss of response to TKI therapy 3. Disease progression to the accelerated or blast phase 4. Relapsed/refractory disease	**Note:** If a multigene panel is performed, appropriate panel codes should be used. back to top **Myeloproliferative Neoplasms (MPNs) Panel Tests** XVII. Myeloproliferative neoplasm (MPN) molecular profiling panel (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) such as a serum erythropoietin level below the reference range for normal B. A targeted (not comprehensive) panel including at a minimum *JAK2*, *CALR*, *MPL*. Note that *BCR/ABL1* can be included as a part of a panel or ordered separately when appropriate XVIII. Myeloproliferative neoplasm (MPN) molecular profiling panel (81219, 81270, 81279, 81338, 81339) analysis is considered **investigational** for all other indications. back to top **Single-Gene Testing Of Solid Tumors And Hematologic Malignancies** **Tumor Specific BCR/ABL Kinase Domain Analysis** XIX. 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. **Any** of the following: 1. Initial response to TKI therapy is inadequate 2. Loss of response to TKI therapy 3. Disease progression to the accelerated or blast phase 4. Relapsed/refractory disease

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Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis XX. Tumor specific *BCR/ABL1* quantitation and breakpoint analysis (0016U, 0040U, 81206, 81207, 81208) in hematologic malignancies may be considered **medically necessary** when **either** of the following criteria is 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 workup for or to monitor disease progression of **any** of the following: 1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myelogenous leukemia (CML) 4. B-cell lymphoma back to top	**Tumor Specific BCR/ABL Quantitation and Breakpoint Analysis** XX. Tumor specific *BCR/ABL1* quantitation and breakpoint analysis (0016U, 0040U, 81206, 81207, 81208) in hematologic malignancies may be considered **medically necessary** when **either** of the following criteria is 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 workup for or to monitor disease progression of **any** of the following: 1. Acute lymphoblastic leukemia (ALL) 2. Acute myeloid leukemia (AML) 3. Chronic myelogenous leukemia (CML) 4. B-cell lymphoma back to top
Tumor Specific *BRAF* Variant Analysis XXI. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when the member: A. Has a diagnosis of **any** of the following: 1. Suspected or proven metastatic, synchronous or metachronous colorectal cancer 2. Advanced or metastatic non-small-cell lung cancer (NSCLC), 3. Stage III or stage IV cutaneous melanoma 4. Indeterminate thyroid nodules requiring biopsy 5. Anaplastic thyroid carcinoma or locally recurrent advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma 6. Low-grade glioma or pilocytic astrocytoma, **OR** B. Is being evaluated for Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype)	**Tumor Specific *BRAF* Variant Analysis** XXI. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when the member: A. Has a diagnosis of **any** of the following: 1. Suspected or proven metastatic, synchronous or metachronous colorectal cancer 2. Advanced or metastatic non-small-cell lung cancer (NSCLC), 3. Stage III or stage IV cutaneous melanoma 4. Indeterminate thyroid nodules requiring biopsy 5. Anaplastic thyroid carcinoma or locally recurrent advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma 6. Low-grade glioma or pilocytic astrocytoma, **OR** B. Is being evaluated for Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype)
Tumor Specific *BRCA1/2* Variant Analysis	**Tumor Specific *BRCA1/2* Variant Analysis**

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XXII. Somatic *BRCA1/2* variant analysis, (full sequence and duplication deletion 81162) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **either** of the following: A. Ovarian, fallopian tube and/or primary peritoneal cancer B. Metastatic prostate cancer	XXII. Somatic *BRCA1/2* variant analysis, (full sequence and duplication deletion 81162) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **either** of the following: A. Ovarian, fallopian tube and/or primary peritoneal cancer B. Metastatic prostate cancer
XXIII. Partial or serial analyses (81163, 81164, 81165, 81166, 81167, 81216) are considered **not medically necessary**.	XXIII. Partial or serial analyses (81163, 81164, 81165, 81166, 81167, 81216) are considered **not medically necessary**.
Tumor Specific *CALR* Variant Analysis XXIV. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when the member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.	**Tumor Specific *CALR* Variant Analysis** XXIV. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when the member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts.
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Tumor Specific CEBPA Variant Tests XXV. Tumor specific *CEBPA* variant analysis (81218) for hematologic malignancies may be considered **medically necessary** when the member has cytogenetically normal acute myeloid leukemia (AML).	**Tumor Specific CEBPA Variant Tests** XXV. Tumor specific *CEBPA* variant analysis (81218) for hematologic malignancies may be considered **medically necessary** when the member has cytogenetically normal acute myeloid leukemia (AML).
Tumor Specific *EGFR* Variant Analysis XXVI. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when the member has a diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following: A. Lung adenocarcinoma B. Large cell lung carcinoma C. Squamous cell lung carcinoma D. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS)	**Tumor Specific *EGFR* Variant Analysis** XXVI. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when the member has a diagnosis of advanced (stage IIIb or higher) or metastatic disease for **any** of the following: A. Lung adenocarcinoma B. Large cell lung carcinoma C. Squamous cell lung carcinoma D. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS)
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Tumor Specific *FLT3* Variant Analysis	

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XXVII. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) for hematologic malignancies may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has cytogenetically normal acute myeloid leukemia (AML) B. Has a diagnosis of acute lymphocytic leukemia (ALL) C. Has a diagnosis of myelodysplastic syndrome (MDS)	**Tumor Specific *FLT3* Variant Analysis** XXVII. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) for hematologic malignancies may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has cytogenetically normal acute myeloid leukemia (AML) B. Has a diagnosis of acute lymphocytic leukemia (ALL) C. Has a diagnosis of myelodysplastic syndrome (MDS)
Tumor Specific *IDH1* and *IDH2* Variant Analysis XVIII. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of a glioma. back to top	**Tumor Specific *IDH1* and *IDH2* Variant Analysis** XVIII. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of a glioma. back to top
Tumor Specific IGHV Somatic Hypermutation Analysis XXIX. Tumor specific *IGHV* somatic hypermutation analysis (81263) in hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) B. Primary cutaneous B-cell lymphoma C. Mantle cell lymphoma D. Post-transplant lymphoproliferative disorder back to top	**Tumor Specific IGHV Somatic Hypermutation Analysis** XXIX. Tumor specific *IGHV* somatic hypermutation analysis (81263) in hematologic malignancies may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) B. Primary cutaneous B-cell lymphoma C. Mantle cell lymphoma D. Post-transplant lymphoproliferative disorder back to top
Tumor Specific*JAK2* Variant Analysis XXX. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** for **any** of the following: A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) such as a serum erythropoietin level below the reference range for normal B. The member has acute lymphoblastic leukemia	**Tumor Specific*JAK2* Variant Analysis** XXX. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** for **any** of the following: A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia) such as a serum erythropoietin level below the reference range for normal

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C. The member is suspected to have a myelodysplastic syndrome	B. The member has acute lymphoblastic leukemia C. The member is suspected to have a myelodysplastic syndrome
Tumor Specific *KIT* Targeted Variant Analysis XXXI. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when the member has **any** of the following: A. Suspected to have, or is being evaluated for, systemic mastocytosis B. A diagnosis of acute leukemia C. Stage IV cutaneous melanoma D. A suspected or confirmed gastrointestinal stromal tumor (GIST)	**Tumor Specific *KIT* Targeted Variant Analysis** XXXI. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when the member has **any** of the following: A. Suspected to have, or is being evaluated for, systemic mastocytosis B. A diagnosis of acute leukemia C. Stage IV cutaneous melanoma D. A suspected or confirmed gastrointestinal stromal tumor (GIST)
Tumor Specific KRAS Variant Analysis XXXII. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has suspected or proven metastatic, synchronous or unresectable metachronous colorectal cancer B. Is undergoing workup for metastatic non-small cell lung cancer C. When included in a panel approved for other indications	**Tumor Specific KRAS Variant Analysis** XXXII. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria: A. Has suspected or proven metastatic, synchronous or unresectable metachronous colorectal cancer B. Is undergoing workup for metastatic non-small cell lung cancer C. When included in a panel approved for other indications
XXIII. Somatic *KRAS* variant analysis (81275, 81276) in solid tumors is considered **investigational** in all other situations. back to top	XXIII. Somatic *KRAS* variant analysis (81275, 81276) in solid tumors is considered **investigational** in all other situations. back to top
Tumor Specific *MGMT* Methylation Analysis XXIV. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when the member has a high grade glioma (stage III or IV), including **one** of the following: A. Anaplastic oligodendroglioma B. Anaplastic astrocytoma C. Anaplastic glioma D. Glioblastoma	**Tumor Specific *MGMT* Methylation Analysis** XXIV. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when the member has a high grade glioma (stage III or IV), including **one** of the following: A. Anaplastic oligodendroglioma

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Tumor Specific MLH1 Methylation Analysis XXXV. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when the member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND** previous tumor testing showed loss of *MLH1* protein expression on immunohistochemistry (IHC) analysis. **Tumor Specific MPL Variant Analysis** XXVI. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when the member displays clinical symptoms of a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts. **Tumor Specific Microsatellite Instability (MSI) Analysis** XXVII. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Colorectal cancer B. Endometrial cancer C. Gastric cancer D. Pancreatic cerncer E. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer F. Recurrent, progressive or metastatic cervical cancer G. Testicular cancer (nonseminoma) and has had progression after high dose chemotherapy or third-line therapy H. Unresectable or metastatic gallbladder cancer I. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma J. Unresectable or metastatic breast cancer K. Small bowel adenocarcinoma L. Metastatic occult primary	B. Anaplastic astrocytoma C. Anaplastic glioma D. Glioblastoma **Tumor Specific MLH1 Methylation Analysis** XXXV. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when the member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND** previous tumor testing showed loss of *MLH1* protein expression on immunohistochemistry (IHC) analysis. **Tumor Specific MPL Variant Analysis** XXVI. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when the member displays clinical symptoms of a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), such as chronically elevated red blood cell counts. **Tumor Specific Microsatellite Instability (MSI) Analysis** XVIII. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Colorectal cancer B. Endometrial cancer C. Gastric cancer D. Pancreatic cancer E. Locally advanced, recurrent or metastatic esophageal and esophagogastric junction cancer F. Recurrent, progressive or metastatic cervical cancer G. Testicular cancer (nonseminoma) and has had progression after high dose chemotherapy or third-line therapy H. Unresectable or metastatic gallbladder cancer I. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma J. Unresectable or metastatic breast cancer K. Small bowel adenocarcinoma

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Tumor Specific NPM1 Variant Analysis XVIII. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when the member has cytogenetically normal acute myeloid leukemia (AML). back to top XXXIX. Genetic testing for *FLT3* tyrosine kinase domain (*FLT3*-TKD) variants is considered **investigational**. **Tumor Specific NRAS Variant Analysis** XL. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when the member has suspected or proven metastatic, synchronous or metachronous colorectal cancer. **Tumor Specific PIK3CA Variant Analysis** XLI. Tumor specific *PIK3CA* variant analysis (81309, 0155U, 0177U) in solid tumors may be considered **medically necessary** when the member has **either** of the following: A. Recurrent or stage IV, HR positive, HER2 negative invasive breast cancer B. A diagnosis of uterine rhabdomyosarcoma. **Tumor Specific RET Variant Analysis** XLII. Tumor specific *RET* variant analysis (81404, 81405, 81406) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria: A. A diagnosis of medullary thyroid cancer B. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma C. To predict treatment response (e.g., pralsetinib [Gavreto] or selpercatinib [Retevmo]) in patients with metastatic NSCLC **Tumor Specific TP53 Variant Analysis**	L. Metastatic occult primary **Tumor Specific NPM1 Variant Analysis** XVIII. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when the member has cytogenetically normal acute myeloid leukemia (AML). back to top XXXIX. Genetic testing for *FLT3* tyrosine kinase domain (*FLT3*-TKD) variants is considered **investigational**. **Tumor Specific NRAS Variant Analysis** XL. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when the member has suspected or proven metastatic, synchronous or metachronous colorectal cancer. **Tumor Specific PIK3CA Variant Analysis** XLI. Tumor specific *PIK3CA* variant analysis (81309, 0155U, 0177U) in solid tumors may be considered **medically necessary** when the member has **either** of the following: A. Recurrent or stage IV, HR positive, HER2 negative invasive breast cancer B. A diagnosis of uterine rhabdomyosarcoma. **Tumor Specific RET Variant Analysis** XLII. Tumor specific *RET* variant analysis (81404, 81405, 81406) in solid tumors may be considered **medically necessary** when the member meets **any** of the following criteria: A. A diagnosis of medullary thyroid cancer B. Anaplastic thyroid carcinoma or locally recurrent, advanced and/or metastatic papillary, follicular or Hurthle cell thyroid carcinoma C. To predict treatment response (e.g., pralsetinib [Gavreto] or selpercatinib [Retevmo]) in patients with metastatic NSCLC

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XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when the member has **either** of the following: A. A diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) B. Is undergoing diagnostic workup for mantle cell lymphoma (MCL) back to top	**Tumor Specific TP53 Variant Analysis** XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when the member has **either** of the following: A. A diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) B. Is undergoing diagnostic workup for mantle cell lymphoma (MCL) back to top
Measurable (Minimal/ Molecular) Residual Disease (MRD) Analysis for hematologic neoplasms **Hematologic Minimal Residual Disease (MRD) Testing** XLIV. Measurable (minimal/ molecular) residual disease analysis (0171U, 81479) in bone marrow or peripheral blood for hematologic neoplasms may be **medically necessary** when the member has a diagnosis of **any** of the following: A. Acute Lymphocytic Leukemia (ALL) B. Multiple Myeloma C. Chronic Lymphocytic Leukemia	**Measurable (Minimal/ Molecular) Residual Disease (MRD) Analysis for hematologic neoplasms** **Hematologic Minimal Residual Disease (MRD) Testing** XLIV. Measurable (minimal/ molecular) residual disease analysis (0171U, 81479) in bone marrow or peripheral blood for hematologic neoplasms may be **medically necessary** when the member has a diagnosis of **any** of the following: A. Acute Lymphocytic Leukemia (ALL) B. Multiple Myeloma C. Chronic Lymphocytic Leukemia
Solid Tumor Minimal Residual Disease (MRD) Testing XLV. Measurable (minimal) residual disease (MRD) analysis (0229U, 0340U, 0306U, 0307U, 81479) in solid tumor tissue is considered **investigational**. back to top	**Solid Tumor Minimal Residual Disease (MRD) Testing** XLV. Measurable (minimal) residual disease (MRD) analysis (0229U, 0340U, 0306U, 0307U, 81479) in solid tumor tissue is considered **investigational**. back to top
Tumor Mutational Burden (TMB) XLVI. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Recurrent or metastatic breast cancer B. Recurrent, progressive or metastatic cervical cancer C. Unresectable or metastatic gallbladder cancer D. Unresectable or metastatic extrahepatic cholangiocarcinoma	**Tumor Mutational Burden (TMB)** XLVI. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when the member has a diagnosis of **any** of the following: A. Recurrent or metastatic breast cancer B. Recurrent, progressive or metastatic cervical cancer C. Unresectable or metastatic gallbladder cancer

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E. Suspected metastatic malignant occult primary tumor F. Recurrent ovarian/fallopian tube/primary peritoneal cancer G. Metastatic or advanced pancreatic adenocarcinoma H. Metastatic castration-resistant prostate cancer I. Progression of testicular cancer (nonseminoma) after high dose or third line therapy J. Endometrial carcinoma or uterine sarcoma **Red Blood Cell Genotyping In Multiple Myeloma** XLVII. Red blood cell genotyping (0001U) in individuals with multiple myeloma may be considered **medically necessary** when the member has **both** of the following: A. A diagnosis of multiple myeloma B. Currently being treated or will be treated with Daratumumab (DARA) **Cancer Exome Sequencing** LVIII. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0329U, 81415, 81416, 81425, 81426) is considered **investigational** unless part of another approved test. back to top **Genetic Testing To Confirm The Identity Of Laboratory Specimens** XLIX. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266,), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance. back to top	D. Unresectable or metastatic extrahepatic cholangiocarcinoma E. Suspected metastatic malignant occult primary tumor F. Recurrent ovarian/fallopian tube/primary peritoneal cancer G. Metastatic or advanced pancreatic adenocarcinoma H. Metastatic castration-resistant prostate cancer I. Progression of testicular cancer (nonseminoma) after high dose or third line therapy J. Endometrial carcinoma or uterine sarcoma **Red Blood Cell Genotyping In Multiple Myeloma** XLVII. Red blood cell genotyping (0001U) in individuals with multiple myeloma may be considered **medically necessary** when the member has **both** of the following: A. A diagnosis of multiple myeloma B. Currently being treated or will be treated with Daratumumab (DARA) **Cancer Exome Sequencing** LVIII. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0329U, 81415, 81416, 81425, 81426) is considered **investigational** unless part of another approved test. back to top **Genetic Testing To Confirm The Identity Of Laboratory Specimens** XLIX. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266,), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance. back to top